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# ANNALS OF INTERNAL MEDICINE

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*Issued Monthly*

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# ANNALS OF INTERNAL MEDICINE

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# The Problem of Pseudo-Syphilis*

By John H Stokes, M.D., *Philadelphia, Pa.*

We are but lately come from the day when the first duty of a syphilologist was to emphasize the importance of a high degree of chronic suspicious alertness towards the omnipresence and the difficulties of recognition of syphilis. In many situations, and in certain groups and communities, that day is certainly not passed. There can be no doubt that emphasis on this aspect of the problem of diagnosis has been and still is well placed. But it is to the credit both of the revived teaching of syphilology and of the conscious effort of the practicing physician to keep abreast of the best his time affords, that the proportion of undiagnosed syphilis is probably materially on the wane. Coincidently with this improvement in diagnostic standards there is developing the usual secondary wave of qualification and reappraisal of diagnostic methods on the one hand, and a wave of over-enthusiasm in the use of certain of them, on the other. There can be very little doubt that today as a result of wholesale application of single diagnostic procedures there is a good deal of syphilis diagnosed which is not syphilis at all. In some instances the difficulty is an obvious one. Error in the performance of some essential test throws the diagnostician off the track and raises suspicions which can be stilled only by the institution of treatment as a therapeutic test, if nothing more. On other occasions the extraordinary facility with which syphilis apes every disease in any field of medicine leads inevitably to a borderline of confusion in which not only one but a number of really very presentable reasons can be urged for regarding a patient as syphilitic when as a matter of fact he does not have the disease. The x-ray picture of a bone, as you shall see; the feel of a liver; nodules in a testis; an incisor tooth, may be the point on which a diagnosis seems to turn. These more genuinely complicated pictures of pseudo-syphilis form the fascinating diagnostic problems which an observer of syphilis endeavoring to apply a general knowledge of the biology of the infection is constantly obliged to confront. Perhaps it is because my practice in the last four years has offered what seems to be unusual opportunities to witness the contestable or the mistaken diagnosis of syphilis, that I feel this problem important enough for attention this evening. On the other hand, at least one competent ob-

*Read before the Academy of Medicine and affiliated societies, Rochester, N. Y., January 2, 1929. From the Department of Dermatology and Syphilology, School of Medicine, University of Pennsylvania.

server has preceded me into the field, in the person of Herbert Mitchell,[1] who now nearly two years ago directed attention to the importance of false laboratory reports in fastening a mistaken diagnosis of syphilis upon numbers of patients. In giving you my impressions of this genuine problem in every-day syphilology I should like to take up the matter under four heads with appropriate case illustrations, which deal (1) with the laboratory sources of error and their control; (2) the biologically false serologic report; (3) the non-specific therapeutic test; and (4) an example of the clinical story of a typical pseudo-syphilis.

*The Laboratory Sources of Error*: It should be axiomatic that no serologic laboratory, no matter how well and conscientiously conducted, is ever always right in its positive reports. The incidence of false positiveness probably ranges somewhere between ½ of 1 per cent and 2 per cent in the properly controlled laboratory. Errors occur in waves and can have a tendency toward false positives or false negatives. In viewing a graph this summer at Geneva representing the accumulated experience of what is probably the most thoroughgoing comparative check of serologic procedures that has ever been made, that of the Conference on Biological Standards under the auspices of the Health Organization of the League of Nations in Copenhagen last June, the proportion of false or non-specific positives obtained by some of the older Wassermann procedures, even with multiple antigens, appeared alarming and almost unbelievable. It applied, not alone to partial positives and weak positives, which everyone today should have learned to regard with caution, but even to strongly positive serologic results. If under the relatively controlled conditions of such a comparative study, 35 per cent of the reports by a certain procedure can be non-specific, it can be readily imagined that under less controlled conditions there must be laboratories which are veritable mills of false reports, fastening suspicion of syphilitic infection right and left upon persons who do not have the disease. In my text-book presentation of this matter I insisted on a differentiation between biologic false positives and technical false positives. The technical false positive arises over and over in laboratories in which the general level of technical excellence may be high but in which it is not possible to control every single one of the innumerable details which are factors in a serologic result. The older types of Wassermann procedure are full of such possibilities of error, and even the newer, simplified and more exactly defined tests are by no means devoid of them. I have known the mere position of a rack of tubes in relation to the freezing coil in an ice-box to cause my staff a week of hard work in unravelling a series of false positives. The controls commonly employed do not have the infallibility with which the laboratory man is inclined at times to credit them. Records do at times get twisted and it does actually seem as if even so remote a thing as the woman technician's menstrual period sometimes had a definite relation to the return of a batch of anomalous and

uninterpretable results. I refrain of course from mentioning the obvious sources of false results, such as dirty glass-ware, careless handling of reagents, too frequent bleeding of depleted animals, failure to control the titer of reagents, and so forth. A point I wish to insist on is that even the technically good laboratory will find constantly arising within itself one or another of these sources of error in serologic reports. Sheplar, Lyons and MacNeal[2] less than a month ago used the admirable phrase "serologic discord" in speaking of the astonishing range of variation in parallel tests of various kinds performed on the serum of patients with late syphilis. While there is in general a high proportion of freedom from error in any of the serologic procedures performed on early syphilis and in persons who do not have syphilis, persons who may have syphilis in its latent or later stages are subject to the full technical vicissitudes of the test.

Take as a general example of the situation with which the consultant finds himself all too frequently confronted the following:

Case 1—A man of 53 years of age whom I personally examined in March 1927 exhibited the clinical symptomatology of a very early paresis with a Kolmer blood Wassermann reaction of 32200, and a Kahn of 444, a spinal fluid of 4444 to 0.2 and 0.4 c.c., a strongly positive Pandy, 5 cells and a colloidal mastic of 5555543210. Owing to some technical difficulties encountered by the home physician in treating his case, he had only a very moderate amount of treatment while away, which could not possibly have changed his serologic reactions materially. A letter received from the physician who dealt with the technical complication and took over his case, reads as follows:

"He was suffering from an injection abscess of the buttock. We opened it and drained about three pints of sterile pus. He has made a good recovery. His blood and spinal fluid are negative. If you have any suggestions relative to future treatment I would welcome them very heartily."

Experience with the biology of the disease, that stabilizing and determining factor which I shall mention more than once again, led me to doubt the accuracy of this report on blood and fluid though I had every personal confidence in the man who quoted it. I requested that the patient see me again. He confirmed the statement that a spinal puncture had been done in the home hospital with a negative report, but I none the less insisted upon and performed a second spinal fluid examination, drawing enough to have the test completely controlled by two laboratories and checking the blood at the same time. The results were as follows:

The spinal fluid examination performed in Kolmer's laboratory and my own, simultaneously, yielded the following results respectively: Kolmer Wassermann 44300, globulin weakly positive, cells 5, gold sol 5553200000; and Kolmer Wassermann 3444, globulin negative, cells 5, mastic 5432100000. The two reports, as you see, are almost identically positive, not negative. The Kolmer Wassermann and Kahn tests

on the blood were likewise strongly positive.

Imagine now the situation in which I found myself—certainly not one to endear me to the home folks, for who is less beloved than he who revealeth an error? If, accepting the report of the home physician's hospital on this patient's serology, I had proceeded to advise further in regard to his treatment without a re-examination, the patient would have gone from bad to worse. Whether the totally mistaken report of the home authority was the result of accidental transposition of specimens, or a gross and total miscarriage of technic, could only be decided by an investigation which I as a consultant could not possibly make. I was obliged instead to resort to the most devious hypothetical possibilities in explanation, such as the transient effect of a Netter's abscess, to save the face of the situation in the eyes of those concerned. This man's life literally hung on the inaccuracy of this particular report. He is now again under treatment for serologically active paresis and has had a third spinal fluid examination to confirm the positive results on the first and second.

Let me cite you another example from a number of typical ones gathered within the last two years.

Case 2—A young man was sent to me with a diagnosis of syphilitic diarrhea and a report of a strongly positive blood Wassermann test said to have been performed by two laboratories simultaneously on specimens of serum drawn at the same time. It would seem that every precaution had been taken to secure the accuracy of the result. He was placed under treatment for syphilis and grew rapidly worse instead of better. In bringing his docket of reports to me, he carried with him the originals of his Wassermann reports. From these it appeared probable that the two specimens of blood drawn simultaneously had been inadvertently sent to the same laboratory instead of two different laboratories. The referring physician insisted, and perhaps rightly, that two laboratories had both reported positive —in which case we may of course have been dealing with a biologic false positive or non-specific result. A total of five different Wassermann tests had, however, according to the reports at hand, been performed in one of the laboratories at the same time, on two blood specimens and all of them had apparently yielded positive results. The institution of treatment, of course, will leave the issue permanently unsettled. Clinically, the patient shows no evidence of syphilis, prenatal or acquired, and has no history of it, nor has my laboratory or a second serologic laboratory been able to find the slightest trace of positive tendency in any specimens of the serum drawn since that time. Again the biology of the disease is the factor which first arouses suspicion. Intestinal syphilis and syphilitic diarrhea is so rare that I have seen only one authentic and one suspicious case in half a lifetime spent in watching for it. The most thoroughgoing examination of the patient, his entire personal and historical makeup and every other detail on which a clinician would check the result of the serologic procedure, is absolutely negative. In fact, it is quite unbelievable

that he has syphilis. He has amebic diarrhea. This man was by no means the victim of diagnostic incompetence. He was examined by men of exceptional ability and his serologic tests performed in a private laboratory which has the confidence of its patrons and is under excellent medical direction. Yet I suspect something slipped and that the patient was placed in the puzzling situation in which he now rests on the basis of a non-specific or a false positive developing in five Wassermanns all done in the same laboratory at the same time.

I could go on for the full extent of my allotted time detailing to you illustrations of similar occurrences in other types of cases. The upshot of the whole matter is this: no laboratory is ever always right when it reports even a strongly positive Wassermann by numerous antigens. The laboratory may be right but the Wassermanns wrong for the patient may not have syphilis. No single positive Wassermann should ever be accepted as evidence of syphilis under any circumstances. No repeatedly positive Wassermann reaction should be accepted as evidence of syphilis on its face. It is always permissible to question any kind of serologic report and no laboratory is entitled or really wishes to be regarded as sacrosanct and above question. A careful clinical inquiry is invariably necessary whenever syphilis becomes a diagnostic possibility and the Wassermann in that inquiry takes rank as a symptom and nothing more. It may be advisable to accept it as the basis for treatment, but in doing so its debatable character must never be wholly lost sight of.

*The True Non-Specific Sources of Serologic Error*: We have been talking thus far about technical sources of error. Let us consider now for a few moments the biological, and hence more or less inevitable, sources of error in the serologic diagnosis of syphilis. In this problem I have been interested for a number of years and have had at least one unusual opportunity to follow through a life-time of anomalous Wassermann reports to the autopsy table. The conventionally accepted true non-specific blood Wassermann reactions occur or are said to occur in the following conditions:

Biologically False or True Non-Specific Positive Blood Wassermann Reactions[2]

1. Frambesia or yaws.
2. Lepra.
3. Tuberculosis.
4. The acute exanthemata.
5. Pneumonia, septicemia (subacute bacterial endocarditis).
6. Trypanosomiases.
7. Relapsing fever.
8. General anesthesia.
9. Advanced malignant cachexia, especially hepatic.
10. Pernicious anemia.
11. Malaria.
12. Pregnancy.
13. Weil's disease.
14. Diabetes (?)
15. Systemic mycotic infections (?)

Of this rather large and incompletely investigated group my experience has been chiefly concerned with latent tuberculosis and with septic infections as apparently productive of false positive serologic reactions in combination with clinical pictures so confusing that a complete evaluation of the situation in the individual case

is sometimes impossible. I can perhaps best particularize by examples.

Case 3—A member of a Catholic Sisterhood, in late middle life, was under my observation for a period of six years and for a number of years preceding had had repeated strongly positive blood Wassermann reactions. These earlier tests had been performed by a standard Wassermann system with a comparatively low degree of sensitivity and responsible for the reporting of more false negatives than positives. Notwithstanding this fact, there was no question that this woman had repeated and conclusive evidence from the serologic standpoint that she had syphilis. On the other hand, the strongly positive Wassermanns were interspersed from time to time with equally indubitable and complete negatives of the most unaccountable sort, bearing little or no relation to her previous treatment and little or no relation to her general condition. Unfortunately she died with the symptoms of a septic endocarditis before the Kolmer Wassermann and Kahn technics came into general use so that it is not possible to compare the results during her decade of ordinary serologic testing with any of the newer methods. The Wassermann procedure used in her case over a period of years, however, varied in no essential particulars from technics still in common use today in many private and institutional laboratories of this country. At autopsy the most thoroughgoing search for evidence of syphilis was made (excluding, however, tissue search for Sp. pallida) and absolutely nothing confirmatory of the existence of the disease was found. The woman was a virgin, absolutely without clinical signs of prenatal infection and presented gross and abundant evidence of a lifetime marred by two interacting afflictions, an extensive tuberculosis of the hilus of the lung and a recent superimposed on an old vegetative endocarditis. From time to time in periods of debility the existence of the endocarditis had been suspected, but the tuberculosis had never crossed the threshold of clinical recognition and had only been included in her life record of clinical diagnoses because she developed from time to time showers of what appeared to be a cutaneous papulonecrotic tuberculid. On the basis of this case and a number of others which I saw previously I directed attention in my earlier publications on tuberculids to the true nonspecific positive Wassermann as a factor of error in the diagnosis of syphilis and of tuberculosis. Of late the field of my observation has swung more towards the septic infection side of this combination. While I recognized clearcut and repeated false positive Wassermanns as occurring in subacute bacterial endocarditis in the febrile patient, I have recently seen a number of cases suggesting that septic and infectious interludes with complete recoveries may in some individuals give rise to unaccountable isolated and even repeated non-specific positive Wassermann reports. As an illustration of the uncertainties introduced into a given case by this possibility—(a frank and typical illustration will be found in Figure 694 of my text[4])—let the following history serve:

Case 4—A man of 48, whose wife is in good health and has two children and no miscarriages, lost rapidly in general condition during the month of September of the past year. In the latter part of August he had had what was thought to be grippe, with considerable fever ranging from 100 to 101°. Coincidently with the onset of the "grippe" he developed what was thought to be a large gland or lump in the skin below the ramus of the right jaw, which lasted for a week, and which the patient thought was the beginning of a carbuncle, for he had had two previous experiences with lesions of this sort on the nape of the neck. On questioning he recalled that a barber some time during the month of July had nicked the skin in this neighborhood in shaving him, but that the nick healed promptly, no ulcer forming. There was no lesion in the mouth. His first blood Wassermann reaction was taken about a month after the onset of the decline in health and was said to have been positive in one of the larger state laboratories, the degree, however, not mentioned. A second test taken immediately was reported negative by one of the best known serologists in a private laboratory in this country. A third Wassermann done at once by the same man was reported positive. At about the time of the third positive Wassermann an eruption on the skin was noted, very mild in character, which an internist interpreted as a purpura. Massive blood cultures, Widal test, and so forth, were performed with negative results, but the blood Wassermann reaction was again strongly positive in a hospital laboratory operated without clinical control. In the examination in which the purpuric eruption was recognized, a definite systolic murmur without cardiac enlargement was detected. Several previous examiners agree that this murmur had not been present in any previous examination. Treatment for syphilis was instituted, and although the eruption was already fading, it was noted that it disappeared completely within twenty-four hours after the first injection of neoarsphenamine. There was, however, no flare-up or Herxheimer reaction. There was no spectacular drop in fever; the patient still has occasional evening chills and runs a temperature ranging from 99.2 to 99.8 at night. There has been a slow but genuine improvement in general health with a continuance of the anti-syphilitic treatment. The blood Wassermann reaction was reported again two weeks after the sixth injection of neoarsphenamine as strongly positive by the same laboratory which had obtained the strong positive during the purpuric phase of the disease. Two weeks later, however, a third clinically controlled laboratory obtained the following results: Kolmer 11, Kahn completely negative, Hinton glycerol cholesterol completely negative, Kline slide test completely negative, this without the intervention of any further treatment or the use of any heavy metal. Physical examination of the patient shows nothing definitely supportive of the diagnosis of syphilis. Exposure is admitted as of a number of years ago and the patient's mother had a remarkable series of miscarriages and stillbirths. The immediate question then is whether the patient's positive

Wassermann is a function of a prenatal, an early or a latent acquired syphilitic infection, perhaps flared up by intercurrent infection, or is a nonspecific positive in the course of a septic dissemination of some organism through the blood stream from which the patient is now gradually recovering? The patient's wife and children are serologically negative. The patient has not had a spinal fluid examination, has no evidence of neurosyphilis, and the spinal fluid examination would be the last thing to commend while he is febrile, for fear of transplanting a possible circulating organism to his meninges. Did the hotel barber implant a syphilitic infection below his right ramus? It is possible, but it seems improbable, though the chronology cannot absolutely negate it. Was the eruption over his thorax and flanks a toxic erythema of streptococcal origin or a secondary syphilid? No one able to make a positive differentiation saw it. At the present time after an amount of treatment which might but probably would not have been responsible for a complete serologic reversal had he an active secondary syphilis, he is still strongly positive to the laboratory which read him positive in the possibly septicemic stage and totally negative even to such sensitive procedures as the Hinton and Kahn when he ought to be strongly positive had he a secondary syphilis. Has he perhaps an old latent syphilitic infection manifesting itself in fever and one of the debility crises that one occasionally sees in the latency of middle life? It is conceivable but difficult to believe. Perhaps he has an early syphilitic aortitis, which may be febrile. Is the systolic murmur part of an endocarditis, or an aortitis, or may it have been functional associated with the fever? The murmur is still present and the fever itself has not responded with the promptitude which I at least have learned to expect in syphilitic fever at all stages of the disease when treated with the arsphenamines. The complete absence of other physical damage ascribable to syphilis at age 48 in a man who has had a latent syphilis for so long a period of years as this one has presumably run, is decidedly out of the ordinary though possible. Equally difficult to explain is the total absence of any stigma of the disease, if this be a prenatal infection. A positive Wassermann, even transient, is, moreover, a rare occurrence in a prenatal syphilis of forty-eight years' standing. With the therapeutic test exhibiting no clearcut result; the serology and the physical findings anomalous and conflicting, the problem for the consultant in such a case becomes one of extraordinary difficulty. Personally I met it by advocating a continuance of treatment appropriate to a recently acquired infection. I do not more than half believe the man has syphilis. But if he has an early syphilis or a syphilitic cardiovascular lesion as early as this, it would be a thousand times better to treat it thoroughly as such than not at all. He is accordingly tolerating very well the routine treatment of an early syphilitic infection. Whether or not he really has syphilis, I question if anyone short of autopsy will ever know.

As an illustration of the discretion which should be used in interpreting the blood Wassermann reaction in pa-

tients who are febrile, due to a possible septic focus, I cite the following:

Case 5—A boy of 17 was hurried to the hospital because of symptoms suggesting an acute appendicitis. For various reasons it was thought inadvisable to operate. A blood Wassermann test, however, was taken as part of the routine examination and returned strongly positive, though the antigenic and technical distinctions are not available. It is stated that he has run bouts of fever, which subside when he goes to bed and recur whenever he endeavors to become active. The boy has been a wayward and peculiar lad in some ways and at one time at the age of 14 was away from home for a period of two weeks, during which his mother thinks it possible he may have suffered venereal exposure. Physical examination shows two small bilaterally symmetrical erosions in the mouth at the dental junction line on the mucosa, which disappeared with the first injection of potassium bismuth tartrate and which were not distinctively specific at the outset. There were one or two slight abnormalities of the osseous system, such as a heavy clavicle and slight thickening and rounding of the anterior aspect of the right tibia, but they were certainly not sufficient to establish a diagnosis of prenatal syphilitic infection. Four days following the first bismuth injection, serologic tests performed in a different laboratory, instead of confirming the strong positives obtained on two occasions while he was in bed with fever, yielded a completely negative Kolmer and a Kahn of 012, which is within the margin of non-specificity of the test. Subsequent Kolmer and Kahn tests, including an immediate repetition, were totally negative in all particulars. Never at any time has there again been a suggestion of positiveness. The mother's blood Wassermann reaction is entirely negative, and there is nothing to substantiate in the family a diagnosis of prenatal syphilitic infection. As I became better acquainted with the boy, I secured what I believe to be a true statement with reference to previous sexual exposure, and none has occurred. We are left, therefore, with a strongly positive Wassermann obtained on two occasions in a single laboratory during a period of confinement to bed with fever, as the sole evidence in favor of the diagnosis of syphilis in this boy's case. Obviously this is a rather slender peg on which to hang two years of treatment procedure and a lifetime of observation. Yet on evidence such as this it is probably safer to proceed with treatment than not to do so, serious though the inconvenience to the patient may be. In thinking of this boy's case I was irresistibly reminded of a young woman whom I observed for a period of years, who suffered from cyclic vomiting and who never could obtain other than a positive blood Wassermann test in a certain laboratory or other than a negative from any other serologist, of whom I had her visit three during the period of my study of her case. In the patient herself and in her entire familial background there was not a scintilla of evidence of syphilis.

The questions and doubts aroused in the mind of the practicing physician

by a recital such as this cannot be resolved by a categorical endorsement or condemnation of one or other type of serologic procedure. Yet you will inevitably want to know just what service the newer modifications and the precipitation tests are performing in dealing with this situation. I think, beginning with the Kolmer modification, all of them represent valuable departures from the established Wassermann technics in the direction of increased sensitivity with due regard for specificity. It is in fact in the older multiple antigen procedures with high cholesterinization that we meet the largest incidence of complexity and partial positive confusion if one can judge by the results of the Conference on Biologic Standards. Sheplar, Lyons and MacNeal have, I believe, offered a very plausible explanation of the situation when they suggest that each procedure, instead of picking out one uniformly and invariably present antigenic substance, interacts with one or another of a number of substances in the production of conflicting or variable positive results. It is highly probable that the non-specific margin of error in all of the serologic tests for syphilis today, arises out of a multiplicity of antigenic substances, some of them not highly specific in origin, which give rise to the conflicts and the dubieties which so impress, not alone the practicing physician but the consulting syphilologist.

It behooves me in rounding out my remarks on this subject to submit to you at least typical instances of the fallibility of the therapeutic test and of the clinical pseudo-syphilis which I mentioned in my introduction.

At one time in discussing the principles underlying the therapeutic test, I emphasized the fact that it should never be performed for a vague or ill-defined group of symptoms and that the non-specific margin of effect of the therapeutic agents employed in the test should be kept constantly in mind. For example, to test a patient therapeutically for syphilis because he has headache and sore throat would be the height of folly, for headache and sore throat are symptoms of innumerable ailments as well as syphilis. Similarly, to test a patient for the syphilitic nature of a macular eruption on the thorax with an arsphenamine is a fundamental mistake, for the macular eruptions most likely to simulate syphilis belong in the toxic erythema group, and toxic erythemas, to say nothing of their spontaneous involution, respond often with astounding promptness to a single injection of neoarsphenamine. You will recall that this was an important interpretative item in the case of the man with fever described above. Agents with a high degree of non-specific effect, such as potassium iodide, should never be used in the precise delineation by therapeutic test of the extent and character of a syphilitic infection. I well recall the general practitioner, who while I was still in medical school gave me the recipe for his success in practice, "If everything else fails, try a little KI; they probably have got syphilis." He made his reputation on that hunch and Heaven only knows how many people with everything ranging from psoriasis to asthma passed through the shadow of suspicion at his hands with curative results. In these days, however, it is

too serious a matter to place a patient in jeopardy of the modern anti-syphilitic therapeutic barrage on the evidence afforded by therapeutic response to something as completely non-specific as iodide. To avoid, then, still another perplexing aspect of non-specific or pseudo-syphilis, it behooves the practitioner to know before he begins a therapeutic test the margin of non-specificity of the drug he proposes to use. Even mercury has a non-specific therapeutic effect. Probably bismuth is today the most available and the least specific of the various employable drugs; yet bismuth will clear up psoriasis and lichen planus and was used within a month as proof of their impossible contentions by that irrepressible group of cranks who insist that all psoriasis is due to syphilis. Just as an illustration of the positive therapeutic test which does not illuminate the diagnosis let me cite the following case. It emphasizes an additional principle as well; that a therapeutic test directed at a non-specific lesion is as likely to give a confusing and non-specific result as if performed with a drug of low specificity for syphilis.

Case 6—A man of 59 with a propulsion gait so marked that he can scarcely totter about; a masked facies suggestive either of the most advanced Parkinsonism or the most degenerated paresis and with a hesitancy in speech that leaves one undecided as to whether he is an extreme example of multiple sclerosis or an almost completely aphasic paresis, is brought to me with a diagnosis of neurosyphilis. The blood Wassermann reaction is negative. The spinal fluid examination, taken immediately following the seizure with which this process began, was negative to the Wassermann procedure, but was said to show a positive globulin, 10 cells and a tabetic gold sol and benzoin curves. Under mercurial inunctions the man got rapidly worse. His neurological examination by Doctor Spiller brings out the statement that a hemorrhage of the basal ganglion would give the same symptoms and findings as this man presents. Such a lesion certainly cannot be regarded as specific and a therapeutic test directed at it cannot be expected to yield other than a non-specific response. Yet within three weeks after the patient is placed on bismuth arsphenamine sulphonate he is walking without a cane; the voice previously inaudible and the speech so retarded that its rate could not exceed ten words a minute is transformed into a reasonably fluent telephone voice, and his facial mask has lost 30 per cent of its fixity. Has this man neurosyphilis and are we resolving a gumma or a vasculitis in the basal ganglion? Not a bit of it. He is simply enjoying the effect, not unfamiliar to those who know their arsphenamine, of an improvement in a Parkinsonian syndrome under this highly non-specific drug used in tonic doses.

As my final contribution to this hour of perplexities I want to offer you a typical illustration of pseudo-syphilis, meaning thereby a disease complex apparently not due to syphilis which none the less presents in its course a series of incidents, in and of themselves rarely seen elsewhere than in syphilis and yet when examined in

the light of the entire story of the case and of a knowledge of the life history of a syphilitic infection, quite obviously non-specific in character and origin. In many difficult cases the sometimes almost indefinable sense of fitness of the syphilologist who has developed an instinct through long experience, is perforce the court of last resort.

Case 7—A woman of 36, a virgin and in previous good health except for nervous disturbances, requested in April, 1926, examination for what was thought to be a urethral caruncle. Immediately upon the discovery and following menstruation, which came on at the same time, she developed what appeared to be an acute infection. The symptoms were those of a severe urethritis, the smears showing a short diplobacillus in two competent laboratories. Following the use of an enema the rectum apparently became infected with the same organism, giving rise to bleeding and pain. Cystoscopy was negative and cautery was used on the caruncle. For a week the patient was much better and then, following repetition of the cautery, pain and burning reappeared. The vagina became involved with severe pain and spasm and the examining physician states that the mucosa was "plush" all the way up into the fornices. This time the patient had fever and two days later while in bed at the hospital her menstruation appeared with a small amount of bloody discharge having an extremely fetid odor. Local treatment of the vagina, with drainage, was carried on from August to October and an eruption of some kind developed of which no clear account can be obtained, associated with vulvar itching. Under continuance of local treatment the patient was comparatively comfortable until March, 1927, when she suddenly developed a gingivitis, followed a week later by symptoms of stiffness, swelling of the neck glands, especially on the right side, and pains in the right and then the left shoulder. A glossitis followed and a painful spot appeared in the left chest. Coincidently a general eruption appeared which was of a florid red, itched somewhat and was accompanied by mouth lesions from which a distinct pellicle or skin could be picked. Patches were most numerous on the gums. A sore spot appeared on the head in the left frontal region with a visible swelling accompanied by fever to 101°F. The mouth lesions finally cleared up. An x-ray of the skull taken in May showed typical ebernation of the inner table of the type frequently observed in lues. Note now the serologic history.

Her blood Wassermann reaction taken at the height of the eruption was negative, a most unusual occurrence for syphilis, though possible. The next blood Wassermann reaction taken when the bone manifestations were observed, showed an anticomplementary Kolmer and strongly positive Kahn, again an unusual occurrence. There were then four or five delayed negatives, part of a provocative procedure. A spinal fluid examination was done and showed a negative Wassermann and colloidal tests but an increased cell count, apparently somewhere between 9 and 19. Diplo-organisms, not gonococci, were found in the vaginal smear. The fever continuing and the patient

definitely ill, the administration of sulpharsphenamine was begun with mercury intramuscularly, but even after six sulpharsphenamine injections and well on into the ensuing rest period, fever continued. It disappeared two weeks after the patient began inunctions. The vaginitis suddenly cleared up following the passage of a large clot of blood in the October menstruation, menstruation having ceased entirely during the three months of acute symptoms.

The patient is now well to all appearances and the serologic tests, both Kolmer and Kahn, are totally negative. The blood viscosity is within normal limits and low for a syphilitic patient who is carrying a false negative. The physical examination of the patient in my office, after the sequence of events above described, yields nothing to support a diagnosis of an active syphilitic infection. The x-ray plates as shown me by the examining physician do unquestionably show bone lesions involving the inner table of the skull of the vertex and frontal regions, which might pass as syphilitic in character and which showed undoubted healing change during the treatment for syphilis which was instituted. At the time of the pulmonary incident a definite small shadow about 3 cm. in diameter and roughly round in shape was observed in the lower right near one of the larger bronchi, but this has since disappeared. The patient is almost hysterical over the tragic possibilities involved in the diagnosis of syphilis and at the same time so syphilophobic as to be absolutely unreserved in all her statements in regard to her history.

Does this young woman have syphilis or does she not? Two able clinicians have told her that they believe she has and it certainly must be confessed that if one saw the x-ray plates alone or heard the patient's account of but a single phase of the situation, the conclusion would be difficult to escape. On the other hand, I believe that a comprehensive survey of the biology of the situation in the light of a knowledge of syphilis in general, justifies the belief that this young woman does not have the disease—even though she has had anti-complementary Kolmers and positive Kahns, which are usually interpreted as strongly suspicious of syphilis, and has had delayed negatives and a rise in spinal fluid cell count to accompany them. To quote from my report on the matter, "this infection, whatever it may be, has not followed a course which my experience or instinct leads me to believe is syphilitic. I believe rather that she has been the victim of a hematogenously disseminated infection of some other type, possibly of a streptococcus or diplo-organism, with invasion by way of the genital tract and the uterus during menstruation and with metastases during the acute phase to the bones of the skull, the lungs and even with a transient slight meningeal reaction. Such transient meningeal reactions in association with various banal infections are well known through the observations of Herrick. I feel that the cutaneous manifestations, though I did not see them, might well be interpreted as on the borderline between erythema multiforme and erythema nodosum and that the mucous membrane lesions as described to me are

more suggestive of this possibility than of syphilis. All things taken together, then, I do not believe that this young woman has the disease. I feel that the therapeutic response exhibited in her case was in all probability nonspecific and in keeping with that seen in erythema multiforme and erythema nodosum and in the bacteremias and septic endocarditides following the administration of an arsphenamine. The question now arises as to whether treatment should be continued. On this point I feel that it is safer to recommend the continuance of antisyphilitic treatment over a reasonable period than to leave this patient's future either to the diagnostic uncertainties of the case or to the prospect of nonspecific recurrence if an aberrant infection still lingers in any tissue of the body."

It would be an injustice to sponsor such a session of diagnostic uncertainties, without proposing at least some means of meeting the situation. What controls can be applied to situations such as these which will leave a firmer ground beneath our feet? In the field of control of laboratory error, it is easier to suggest methods of preventing confusion than in the field of pseudo-syphilis itself. I venture the following suggestions:

1—Never in a doubtful case accept a single serologic report from one laboratory or even two reports performed at the same time in the same laboratory, without an internal check of at least two methods and a repetition.

2—Never accept any serologic report which does not give the degree of positiveness, the antigens and the technic.

3—Never accept a spinal fluid report which does not give the details of all four test procedures: Wassermann, globulin, cell count and colloidal tests. The bane of the consultant's existence is the incomplete spinal fluid report, whether due to too small quantity, blood contamination, shipment conditions or laboratory inadequacy.

4—Refuse any longer to accept a report based on a single type of procedure—i.e., complement fixation only, or precipitation only. For ordinary practice as well as for the expert it is not too much to require both—and 3 or 4 tests of radically different types are often helpful.

5—Never consider a laboratory report as apart from the clinical examination of the case. While the laboratory may furnish the only available evidence of syphilis, the clinical examination and the careful historical appraisal may furnish the only evidence against syphilis, entirely too often to be neglected. A Wassermann is part of a case, not a case in itself.

On the positive side I offer the following:

It is safe to say that there is only one type of laboratory which is adequately controlled from the clinical side, and that is the serologic laboratory which works in cooperation with a syphilis clinic. All other laboratories divorced from the one court of last resort are the inevitable sufferers from factors of error which they can never control or detect by any system of checks and balances within themselves.

Answerable as they are only to inexperienced practitioners and general clinicians with a limited and uncontrolled material in syphilis, their margin of error is certain to be larger and more continuously in evidence than that of a laboratory checked and accountable to a well-organized syphilologic clinic. The small private laboratory operating in two or three rooms in a skyscraper totally divorced from the world of syphilologic practice is the most dangerous source of error with reference to the diagnosis of the disease that exists today, and this statement is true almost regardless of the name and fame of its head. Even inter-laboratory checks cannot adequately control the factors of error in such organizations. They are divorced from the case. It will represent no mean advance when even the great state laboratories are obliged to check themselves continuously against one or more of the established syphilologic clinics in their regional domain.

I wish I could be as simply, and I hope as convincingly, aphoristic in my suggestions for the application of clinical criteria of decision to the patient with pseudo-syphilis as one meets him in the consulting room. The judgment exercised there has an inevitable personal and temperamental quality which is not exactly reducible to control terms. It rests upon the range and penetration of the syphilologist's insight into the life story of the most versatile of all disease simulators and the details of the most varied of pathologic panoramas. A large part of it is subconsciously stored. A balance must be drawn between impressions based on the survey of much material and the instinctively noted landmarks of the individual patient's case. There must be a laying on of hands, *persona propria,* for in contravention of an earlier utterance of my own, something passes through the fingers and the ears and the eyes as one manipulates and searches the patient himself in personal examination, which is of the essence in critical decisions and cannot be inscribed in reports. When such an examination has been made; when complete returns of the laboratory aspects of the work-up from controllable sources are before him, let the arbiter take twenty-four hours. Long before it is up, the subconscious mind may have made the decision, and the hair of his neck may bristle like that of wolf-hound on scent. Yet let him hold himself in leash, and compel the leaping thought to take the slow, the reasoned, the tortoise pace of the written word. Instead of dashing off on an engraved card ready to hand "The diagnosis is syphilis", let him dictate one of these appalling letters, four closely written pages long in which he reveals to the horrified or bored referring practitioner, the tortures of experiential error and the pangs of logical differentiation through which he has given birth to a decision that this person has or does not have syphilis. After that, though as judge he may expose another's error uncharitably, though he may confess bafflement, though he may decide wrongly and be in later months or years reversed—he'll grow, and like the just, he will sleep well.

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# Basal Metabolism in Polycythemia Vera*†

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FOLLOWING the introduction of the Zuntz Geppert method of studying the respiratory metabolism, Senator, Lommel, Tangl, Gordon, Grafe, von Bergmann and Plesch, Rőver, Plehn, Mohr, and Shill reported individual cases in which such studies were made on patients with polycythemia vera. Mosse (1920) collected these and presented them in convenient tabular form. He expressed the data, however, in cubic centimeters of oxygen for each kilogram of body weight. Grafe (1923) in his extensive monograph recalculated the data given by Mosse and stated that, in comparison with the Harris and Benedict normal standards in only six of the twenty-two cases in the literature was the basal metabolic rate increased. Grafe added three carefully studied cases in which the basal metabolic rates were +42, +34, and +33 per cent, and the erythrocyte counts, 8,000,000, 10,600,00 and 7,500,000 respectively. Abbott, Marsh and Isaacs each reported one case of polycythemia vera in which the basal rates were +16, +21, and +31 per cent respectively. Minot and Buckman found that six determinations in four cases varied between +10 and +35 per cent. Brown and Giffin reported that in six cases basal rates were respectively +44, +37, +22, +9, +5, and +4 per cent. Harrop reported a series of fifteen cases, in which the basal metabolic rate varied between +4 and +52 per cent. He stated that in the majority of cases there seemed to be a moderately increased basal rate which was not directly related to the increase in hemoglobin or to the number of erythrocytes, and on which treatment had a variable effect, although the disease was clinically improved. Du Bois stated that polycythemia vera is a condition which may be accompanied by an increase of the basal metabolic rate.

This report is a study of the twenty-three cases seen at The Mayo Clinic in which the basal rate was determined at the time of admission. All were definite cases of polycythemia vera, with a blood volume of 120 c.c. or more to each kilogram of body weight, and with the exception of three cases the spleen was palpable. In these three, the rest of the clinical picture was typical of the disease. Care was taken to exclude from the series cases in which the polycythemia was secon-

*Work done in Division of Medicine and Section on Clinical Metabolism, The Mayo Clinic.

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TABLE I
RESULTS OF DETERMINATIONS IN TWENTY-THREE CASES OF POLYCYTHEMIA VERA

| Case | Basal metabolic rate | Erythrocytes, millions in each cubic millimeter | Hemoglobin, gm. in each 100 c.c. | Whole blood, c.c. for each kilogram of body weight | Blood cells, c.c. for each kilogram of body weight | Whole blood, c.c. for each square meter of body surface | Blood cells, c.c for each square meter | Chief complaint | Symptoms related to vascular distention | Symptoms related to organic changes in blood forming organs | Symptoms related to disturbed metabolism | Incidental complications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | +51 | 8.30 | 21.3 | 191 | 125 | 7485 | 4900 | Pruritus | | | | |
| 2 | +44 | 7.50 | 21.5 | 206 | 129 | 6640 | 4180 | Mass in left upper quadrant | High color | Mass in left upper quadrant | Asthenia, weight loss, gastro-intestinal distress | |
| 3 | +42 | 5.60 | 18.0 | 191 | 107 | 6725 | 3770 | Edema of ankles | High color, slight vertigo | | Asthenia, weight loss of 23 pounds with poor appetite, mild heat intolerance | Adenoma of thyroid gland |
| 4 | +33 | 7.60 | 27.3 | 221 | 170 | 8890 | 6755 | Weight loss of 50 pounds but appetite unchanged, bleeding gums | Bleeding gums | | Weight loss of 50 pounds, with no change in appetite | |
| 5 | +30 | 8.90 | 27.1 | 222 | 155 | 6190 | 4270 | Mass in left upper quadrant | Slight headaches | Mass in left upper quadrant | Heat intolerance | |
| 6 | +29 | 6.50 | 20.0 | 190 | 114 | 7010 | 4200 | Asthenia | High color | | Asthenia, loss of weight, appetite fair, gastro-intestinal distress | |
| 7 | +24 | 6.40 | 22.5 | 183 | 123 | 6470 | 4330 | Asthenia, vertigo, urinary symptoms | Vertigo, paresthesia | | Asthenia | |
| 8 | +22 | 6.30 | 20.4 | 120 | 73 | 4765 | 2880 | Gastro-intestinal distress | | Mass in left upper quadrant | Gastro-intestinal distress | |
| 9 | +22 | 6.70 | 20.1 | 120 | 68 | 5100 | 2890 | Vague gastro-intestinal distress | | | Vague gastro-intestinal distress | Mild diabetes, ovarian cyst |
| 10 | +21 | 7.80 | 27.4 | 202 | 140 | 7890 | 5440 | Asthenia, vomiting | | | Asthenia, gastro-intestinal distress, weight loss of 20 pounds, appetite poor | |
| 11 | +20 | 7.30 | 25.5 | 227 | 159 | 4730 | 3070 | Paresthesia (legs) | High color, pares- | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | appetite poor | | | |
| 11 | +20 | 7.30 | 25.5 | 227 | 150 | 4720 | 2070 | Paresthesia (legs) | High color, paresthesia, headaches | | | |
| 12 | +20 | 5.80 | 21.1 | 136 | 82 | 5200 | 3130 | Pain in legs, high color | High color | | | |
| 13 | +18 | 6.40 | | 224 | 157 | 8070 | 5650 | Edema of legs asthenia | Edema of legs, hemorrhage after extraction of teeth | | Asthenia, weight loss with poor appetite | |
| 14 | +16 | 6.90 | 23.3 | 167 | 119 | 5320 | 3760 | Gastro-intestinal distress, pain in left upper quadrant | Headache, vertigo, scotomas | Pain in left upper quadrant | Gastro-intestinal distress | |
| 15 | +13 | 8.50 | 29.4 | 193 | 139 | 7080 | 5100 | Headache, gastro-intestinal distress | Vertigo, tinnitus | | | Blood pressure systolic 190, diastolic 140 |
| 16 | +10 | 7.30 | | 173 | 119 | 6490 | 4490 | Vertigo | Vertigo, high color | | Asthenia, mild gastro-intestinal distress | |
| 17 | + 9 | 5.50 | | 140 | 92 | 5225 | 3400 | Constricting pain in epigastrium | Loquacious, nervous, tinnitus, headache, high color | | | |
| 18 | + 9 | | 25.6 | 174 | 103 | 5000 | 2800 | Asthenia, loss of weight | High color | Pain in abdomen (not localized) | Heat intolerance, loss of weight, asthenia | |
| 19 | + 8 | 7.50 | 24.2 | 168 | 97 | 5830 | 3500 | Cough, hemoptysis | Nasal hemorrhage, hemoptysis, cough | | Asthenia, loss of weight with poor appetite | Bronchiectasis and fibrosis of lungs |
| 20 | + 8 | 7.00 | 26.0 | 180 | 134 | 7460 | 5600 | Asthenia, renal disorder | Headache, vertigo, high color, bleeds easily from cuts, and so forth | | Asthenia | Adenoma of prostate gland |
| 21 | + 5 | 6.60 | | 128 | 77 | 5180 | 3105 | Vertigo, high color | Vertigo, high color | | Asthenia, gastro-intestinal distress, slight loss of weight | |
| 22 | + 4 | 8.40 | 25.0 | 211 | 156 | 8050 | 6100 | Epigastric pain | High color, irritable | | Gastro-intestinal distress | Duodenal ulcer |
| 23 | + 3 | 7.10 | 25.1 | 176 | 106 | 6165 | 3740 | Mass in right side of abdomen, hematuria, asthenia | High color | | Asthenia, weight loss of 10 pounds with poor appetite | Hypernephroma |

dary, cases of leukemia and cases in which treatment had been given recently. Complicating hyperthyroidism was satisfactorily excluded in all cases except one. This was the case of a woman of seventy-four years, who presented a definite clinical picture of polycythemia, with a blood volume of 191 c.c. for each kilogram of body weight, and a palpable spleen. She also had an adenoma of the thyroid gland which had undergone calcification. Her basal rate was +42 per cent and it was impossible to exclude definitely a mild degree of hyperthyroidism. Harrop, in his review of the subject, was able to find reports of only two cases in which hyperthyroidism could even be suspected of being present; one of these was reported by Tyrrell and the other, by Zadak. Hyperthyroidism is therefore unusual and incidental in these cases. Other incidental complications were present in six of the cases, namely: a mild grade of diabetes and ovarian cyst, essential hypertension with a systolic blood pressure of 190 and a diastolic pressure of 140, duodenal ulcer, bronchiectasis and pulmonary fibrosis, adenoma of the prostate, and hypernephroma.

The series was analyzed to determine whether there was a correlation between the basal metabolic rate, using the Du Bois standards, and the following factors: (1) the blood volume for each unit of body weight; (2) the cell volume for each unit of body weight; (3) the blood volume for each unit of body surface; (4) the cell volume for each unit of body surface; (5) the degree of concentration of the erythrocytes in the peripheral circulation as determined by the routine blood count; (6) the concentration of hemoglobin in grams for each 100 c.c., and (7) the severity, multiplicity or combination of symptoms common in the disease.

Table 1 gives the results of the various determinations in the series. The cases are arranged in the decreasing numerical values of the basal rate. It is seen that the erythrocyte count, the concentration of hemoglobin, and the blood and cell volumes for each unit of body weight and surface area do not likewise fall in an arrangement of decreasing numerical values. Furthermore, there was no semblance of a curve formed, when these factors, individually, were graphically plotted against the basal rate. This evidence, therefore, indicates that a significant correlation does not exist between the basal rate and the factors mentioned, nor with the so-called cardinal symptoms as presented in table 1.

In ten cases of this series, blood volume, basal rate, and erythrocyte determinations both before and after treatment were studied. In cases 3, 12, 14 and 20, as seen in table 2, there was no significant change in the basal rate after treatment, although there was a decided decrease in the volume of blood for each kilogram of body weight as well as in the erythrocyte count. Case 3 was treated by venesection, the others by phenylhydrazine hydrochloride. In case 2, treated with the roentgen ray and venesection, in cases 6 and 8 treated with roentgen ray, and in cases 7 and 10 treated with phenylhydrazine hydrochloride, the basal rate decreased after treatment along with the blood volume for each kilogram of body weight, and along

TABLE 2
BASAL METABOLIC RATE, BLOOD VOLUME, AND NUMBER OF ERYTHROCYTES IN TEN CASES OF POLYCYTHEMIA VERA BEFORE AND AFTER TREATMENT

| | | Before treatment | | | After treatment | | |
|---|---|---|---|---|---|---|---|
| Case | Type of treatment | Blood volume, c.c. in each kilogram of body weight | Basal metabolic rate, per cent | Erythrocytes, millions in each cubic millimeter | Blood volume, c.c. in each kilogram of body weight | Basal metabolic rate, per cent | Erythrocytes, millions in each cubic millimeter |
| 2 | Roentgen ray; venesection | 206 | +44 | 7.50 | 144 | +11 | 6.20 |
| 3 | Venesection | 191 | +42 | 5.60 | 131 | +40 | 4.90 |
| 6 | Roentgen ray | 190 | +29 | 6.50 | 146 | +20 | 4.80 |
| 7 | Phenylhydrazine hydrochloride | 183 | +24 | 6.40 | 103 | − 4 | 2.60 |
| 8 | Roentgen ray | 120 | +22 | 6.30 | 91 | − 4 | 5.00 |
| 10 | Phenylhydrazine hydrochloride | 202 | +21 | 7.80 | 87 | +12 | 2.00 |
| 12 | Phenylhydrazine hydrochloride | 136 | +20 | 5.80 | 71 | +23 | 3.10 |
| 14 | Phenylhydrazine hydrochloride | 167 | +16 | 6.90 | 90 | +15 | 2.00 |
| 15 | Phenylhydrazine hydrochloride | 193 | +13 | 8.50 | 81 | +29 | 3.30 |
| 20 | Phenylhydrazine hydrochloride | 180 | + 8 | 7.00 | 75 | + 4 | |

with the erythrocyte count. In case 15 the basal rate definitely rose after treatment with phenylhydrazine hydrochloride although the blood volume and erythrocyte count dropped. Thus, in five cases there was a drop in the basal metabolic rate after treatment; in one case it rose, and in four cases it was unchanged. Therefore, conclusions cannot be drawn as to the effect of treatment on the basal rate.

## COMMENT

In this series of twenty-three cases of typical polycythemia vera the basal metabolic rates ranged between +3 and +51 per cent prior to treatment. In fifteen of the cases (65 per cent) the rate was above the normal range. There was no evidence that the rate was dependent on, or related to, the increase in the blood and cell volume for each unit of body weight or of surface area. Moreover, the basal metabolic rate bore no relation to the concentration of hemoglobin or erythrocytes; in fact, there does not seem to be any correlation between the metabolic rate and the severity of the disease as evidenced by the general symptoms. Treatment, although it produces a reduction in the blood volumes and cell counts, had a variable effect on the basal metabolic rates.

Various factors have been suggested as the cause of the increased metabolic

rate which frequently but not invariably is found in cases of polycythemia vera. Abbott suggested an increased rate of regeneration of cells. Isaacs, on the basis of high uric acid in his case, believed that the increased rate of metabolism was due to an increase in the amount of nuclear material destroyed; the erythrocytosis accounted for the increased amount of nuclear material that was available for destruction. In the present series, the blood uric acid was determined in only five cases; in all five the basal rate was elevated, but the blood uric acid was normal. Minot and Buckman suggested that the increased rate was dependent on the abnormal blood formation and the presence of immature cells in the circulation. Grafe suggested, but did not subscribe to the belief, that deranged protein metabolism, or abnormal physiologic activity of the spleen and bone marrow might be factors. That an increased blood volume might cause the increased metabolism has been advanced as a theory. Delchef in 1906 experimentally transferred large amounts of blood into dogs, but believed that the increased metabolism was due to the excitability of the animals. This has also been the experience of other observers, so that the evidence for the theory is inconclusive. There is evidently no experimental or clinical proof satisfactory to support any of these theories, and the true cause of the increased production of heat is still a matter of conjecture.

## Summary

In a series of twenty-three cases of polycythemia vera, fifteen patients (65 per cent) had an increase in the basal metabolic rate above the normal range of +10 per cent. An increased production of heat is a frequent, but by no means an invariable, phenomenon.

There is no relation in this series between the basal metabolic rate and the increase in the blood volume, the cell volume, the erythrocyte count, or the concentration of hemoglobin. Furthermore there is no relation between the basal metabolic rate and the syndrome of polycythemia.

The effect of treatment on the basal metabolic rate is variable.

The cause for this tendency toward increased production of heat in this disease is unknown.

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# Hematologic Study of Three Generations of a White Family Showing Elliptical Erythrocytes*

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UNDER normal circumstances the morphology of the red blood corpuscles is so uniform that any deviation is looked upon as evidence of a pathologic state. Everyone is familiar with the striking variations in the size and shape of the erythrocytes in pernicious and severe secondary anemias in which a wide variety of abnormal red cells may be seen but without the predominance of any one form. This is not true for all blood disturbances, however, for instances are recorded in the literature in which there have been observed quite characteristic variations in the shape of the erythrocytes with a preponderance of one type of abnormal cell. In this category belongs sickle cell anemia and the more rarely observed instances of elliptical erythrocytes in the blood of normal persons. In these blood disturbances heredity is apparently an important factor.

The condition now known as sickle cell anemia was first described by Herrick (1) in 1910. A year later Washburn (2) recorded the second instance, also in a negro.

Cook and Meyer (3) who reported the third case in 1915 were the first to point out its familial nature. Emmel (4) studied the blood from the father of Cook and Meyer's patient and noted latent sickling of his erythrocytes. Mason (5) reporting the next instance in 1922 was the first to

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call the disease "sickle cell anemia" and to suggest its racial selectivity. With the publication of the work of Sydenstricker, Mulherin and Houseal (6) and of Huck (7) in 1923 came the first real understanding of this unusual type of anemia. Their investigations showed that the anemic syndrome characterized by sickling of the erythrocytes is relatively common and not, as previously supposed, a medical curiosity. Both demonstrated its constant familial character and apparent limitation to the black race. Their studies further indicated that sickle cell anemia is a definite clinical entity characterized by a clear-cut symptom-complex and by specific blood findings and anatomic changes. Since the appearance of the work of Sydenstricker and Huck many investigators have become interested in the disease as evidenced by the increasing number of reports in the literature of each succeeding year.

(6) Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W., Sickle Cell Anemia, Report of Two Cases in Children with Necropsy in one Case. Am. J. Dis. Child. 26: 132, (Aug.) 1923.

(7) Huck, John G., Sickle Cell Anemia. Bull. Johns Hopkins Hosp. 34:335, (Oct.) 1923.

In negroes the sickling tendency is not rare. Mulherin and Houseal (8) state that Sydenstricker in a study of 1000 negroes found sickle cells in 0.6 per cent, while in an equal number of whites the anomaly was never observed. More recent investigators report a much higher incidence. Cooley and Lee (9) observed sickling in 7.5 per cent of 400 negroes, Graham and McCarty (10) in 7.2 per cent of 608 colored persons and Miyamoto and Korb (11) in 19 of 300 negroes (6.3 per cent). The last named authors found no abnormal cells in 100 white controls.

(8) Mulherin, W. A., and Houseal, R. W., Sickle Cell Anemia from a Pediatric point of view. Tr. Sect. Dis. Child., A. M. A., p. 77, 1924.

(9) Cooley, Thomas B. and Lee, Pearl, The Sickle Cell Phenomenon. Am. J. Dis. Child. 32:334, (Sept.) 1926.

(10) Graham, George S. and McCarty, Sarah H., Notes on Sickle Cell Anemia, J. Lab. and Clin. Med. 12: 536, (March) 1927.

(11) Miyamoto, Kazuo, and Korb, J. H., Meniscocytosis (Latent Sickle Cell Anemia): Its Incidence in St. Louis. South. M. J. 20:912, (Dec.) 1927.

Much rarer are reports of elliptical red blood cells in both white and colored people. The first recorded instance of this anomaly is that of Dresbach (12) in 1904. His subject was a healthy mulatto male 22 years of age in whom 90 per cent of the red blood cells were elliptical in outline. The corpuscles averaged 4.1 $\mu$. in width, 10.3 $\mu$. in length and 2 $\mu$. in thickness, with a ratio of width to length of 1:2.5. No family history was obtainable. A brother of the patient had normal erythrocytes. Dresbach and others who examined the blood believed that the condition was probably congenital in nature. In 1914 Bishop (13) reported a similar case. His patient was a man (color not stated),

(12) Dresbach, Melvin, Science, 19:471, 1904.

(13) Bishop, F. Warner, Elliptical Human Erythrocytes. Arch. Int. Med. 14: 388, 1914.

41 years of age, suffering from acute appendicitis. Routine examination of the blood revealed a polymorphonuclear leukocytosis, 5,400,000 red cells and 110 percent hemoglobin (Fleischl-Meischer). In stained smears there were many elliptical erythrocytes and repeated examinations over a period of several months showed that 75 to 80 percent were elliptical or distinctly elongated. Most of the elliptical cells measured about 13.0 by 5.0 microns. The possibility of mechanical distortion of the corpuscles was considered and eliminated. Suspecting that the abnormality might be hereditary, Bishop studied the blood of all available relatives of the patient consisting of the father, two sisters, and two nephews. Of these one sister, also in good health, exhibited the some blood picture. Bishop regarded this as strong evidence in favor of the condition being a congenital anatomical defect. More recently Huck and Bigalow (14) have described a poikilocy-

(14) Huck, John G. and Bigalow, Rena M., Poikilocytosis in Otherwise Normal Human Blood. (Elliptical Human Erythrocytes) Bull. Johns Hopkins Hosp. 34: 390, (Nov.) 1923.

tosis characterized by the presence of elliptical erythrocytes occurring in a healthy white woman 28 years of age. In the fresh preparations between 53 and 84 per cent of the corpuscles were elliptical or elongated, in hanging drop slides 59 to 70 per cent and in stained smears from 12 to 40 per cent. The average measurements of the cells varied from 12 x 5 $\mu$. in the fresh preparations to 10 x 4 $\mu$. in smears. The hemoglobin percentage, red and white cell counts and platelet counts were normal. A study of fourteen members of the subject's family distributed over four generations disclosed a similar condition in her mother. The authors feel that hereditary transmission, while not definitely established, is strongly suggestive. Huck and Bigalow were able to demonstrate that this was not an instance of sickle cell anemia since the abnormal corpuscles neither increased in number nor changed in form on standing as invariably occurs in sickle cell anemia. On the contrary the cells remained in the same state in which they were first observed until the preparations deteriorated. In Huck's experience with sickle cell anemia, in which more than 50 per cent of the corpuscles acquired bizarre forms on standing, there was an associated secondary anemia which was entirely lacking in this subject although 80 per cent of her cells were abnormal. Their observations show that such a poikilocytosis differs from sickle cell anemia in every respect save the hereditary factor apparently common to both.

Lawrence (15) has reported the

(15) Lawrence, John S., Elliptical and Sickle-Shaped Erythrocytes in the Circulating Blood of White Persons. J. Clin. Investigation, 5:31, (Dec.) 1927.

hematologic findings in a white woman presenting what the author believes to be most of the blood changes generally associated with sickle cell anemia, but which appear to us to conform rather to the elliptical cell anomaly described

by Dresbach, Bishop, Huck and Bigalow and ourselves. His patient was a woman 32 years of age who came to the hospital complaining of disability in walking. She gave a history of soreness of the mouth, bleeding about the teeth for several years, bleeding hemorrhoids for five years and profuse menses lasting from seven to nine days. She was the mother of three children, two of whom were living. Her present illness began ten months before admission to the hospital with a respiratory infection which she thought was influenza, following which she had been tired and weak. The patient appeared pale and undernourished with a slight pallor of the mucous membranes. The erythrocyte count was 3,850,000, hemoglobin 45 per cent (Sahli) and white cells 8,900. In stained smears there was a moderate achromia with rare polychromatophilic cells. Most striking was the decided tendency of the erythrocytes toward sausage forms. The platelets were apparently normal as was the differential white count. In a fresh sealed preparation examined one hour after it was taken most of the erythrocytes were observed to be fairly uniform in size with only a few small and no very large forms. From 5 to 10 per cent of the corpuscles were definitely sickle or sausage-shaped, some showing blunt or rounded ends while others were pointed. On many of the abnormal cells were slender processes from 1 to 10 micra in length which appeared to be attached to the membrane of the cells. In the crescent forms the processes were more marked and often free in the plasma. Rod-shaped bodies thought to be broken-off processes of the abnormal red cells were observed in many leukocytes. No nucleated red cells or myelocytes were found. A brother, one sister and a niece of the patient exhibited the same abnormality of the erythrocytes. Unfortunately ignorance and superstition on the part of the family made impossible any further study of either the patient or her relatives. In a control series of 102 normal white adults sickle-shaped, sausage and filamentous red cells were found three times. In addition evidence of sickling was noted in 6 adult whites and 4 colored adults suffering from various diseases. Definite evidence of latent sickling was lacking in the white subjects but was present in the negroes. Lawrence is uncertain as to the diagnosis of sickle cell anemia in the white woman because no proof of negro blood could be obtained.

### Author's Observations

The family studied consists of Mr. and Mrs. A. Kl., their eight children and six grandchildren. (Chart 1) With the exception of one daughter (Adriana) living in Portland all reside near Missoula, Montana. The distance separating the two cities has made impossible a detailed study of any member except the above mentioned daughter, although one of us (W. C. H.) visited the remainder of the family and from the father, whose blood exhibited the presence of abnormal erythrocytes, obtained the following family history:

So far as known both parents are of pure Dutch stock. There has been no intermarriage with persons from

the Dutch colonies and prior to the emigration of Mr. and Mrs. Kl. to America none of the family had ever been outside the boundaries of Holland. For generations the men were farmers and lived in the village of Zevenhuizen, near Amsterdam. The father knew both his paternal and maternal grandparents and recalls nothing unusual in their color or facial characteristics. On his mother's side a number of aunts and uncles died from unknown causes before reaching middle age. His mother died at 40 from childbirth, his father at 75 from "old age." Two brothers and two sisters are alive and well.

Both Al. K. and his wife enjoy excellent health and neither has ever been seriously ill. In appearance the parents are decidedly Teutonic as are also most of their children and grandchildren. All are fair skinned and exhibit none of the facial characteristics of the black race.

The only member having outspoken symptoms of anemia is Adriana, whose residence in Portland has enabled us to make repeated blood examinations over a period of several months. She gives the following personal history:

Adriana N. Age 25. Married. Registered Nurse.

### Past History

The patient was born in Holland and there spent the early years of her childhood. Her mother states that while she was still quite young an ulcer appeared on her right leg. The lesion was treated by a physician in Amsterdam and healed without difficulty. The cause of the ulcer was undetermined. In childhood she had measles, whooping cough, bronchopneumonia and an attack of arthritis involving the ankle joints. Following this she enjoyed good health but was never robust. In 1918 she had a severe attack of influenza and since then has always felt weak. Upon admittance to a nurses' training school in 1920 it was found that she was anemic, the hemoglobin at that time being only 60 per cent. She was allowed to enter training, however, and although anemic and always "tired out", finished in the usual three years. In 1923 while employed in the laboratory of a Portland hospital a blood examination revealed 3,000,000 red cells with 69 per cent hemoglobin (Dare). The technician who examined the blood noted the presence of abnormally shaped erythrocytes but no further investigation was made at that time.

Prior to tonsillectomy in 1923 the patient suffered from recurrent attacks of tonsillitis. For the past three years she had had bilateral maxillary sinusitis. Two years ago a pyelitis developed which did not clear up for nearly a year.

For a long time she has experienced intermittent attacks of severe pain in the left hypochondrium and gastric distress described as "bilious attacks". At times she feels very well the first part of the day but is tired out by night especially when working. In spite of this she has continued to do her housework and part-time nursing. Numbness and tingling of the extremities has been noted for several years. The patient never sought treatment for the anemia.

Menstruation began at 20 and was irregular until after marriage two years ago. The periods now occur every 28 days, usually lasting 4 days. As a rule the flow is not excessive. There have been no pregnancies.

### Present History

Our attention was first drawn to the case in October, 1927, when one of us (W. C. H.) was asked to examine the differential smear of the patient's blood. At this time (Oct. 3) Mrs. N. was able to work although she felt tired and weak and appeared distinctly anemic.

### Physical Examination.

(Dr. Karl P. Moran)

October 21, 1927.

The patient is well developed and well nourished. There is a distinct cutaneous pallor.

Eyes: sclerae clear; conjunctivae pale; pupils react to light and accommodation.

Ears and nose: negative.

Mouth: mucous membrane pale; several devitalized teeth; tonsils absent; pharynx negative.

Neck: anterior cervical lymph nodes slightly enlarged; thyroid palpable but is soft and not nodular.

Thorax: heart and lungs normal.

Abdomen: area of liver dullness is within normal limits; slight tenderness over gall bladder region; outlines of spleen cannot be percussed or palpated.

Extremities: old scar 1.5 by 2.5 cms. on medial surface of right calf; no palpable enlargement of axillary or epitrochlear lymph nodes.

Pelvic: complete retroversion of uterus; adnexa negative.

Reflexes: all are present but are quite sluggish.

Blood pressure: 118 systolic, 70 diastolic.

Temperature: 98.6° F.

### Hematologic Findings

Examination of stained smears of Mrs. N.'s blood revealed a striking abnormality in the shape of the corpuscles with distinctly elliptical or oval forms predominating. Less numerous were much elongated rod-like or curved sausage-like forms and pear-shaped, sickle-like and other irregularly shaped poikilocytes, often having one or more thin filamentous processes with knob-like ends. Only a small percentage were round. Repeated counts of one thousand cells gave the following average percentage of the different varieties: oval 84.0%, round 0.7%, elongated 5.8%, irregular processed forms 4.5% (See Chart II). Achromia was lacking but some cells exhibited polychromatophilia.

Sealed fresh preparations of the whole blood under number O cover glasses were set up, left at room temperature and examined immediately and at frequent intervals until the erythrocytes disappeared, usually within four to seven days. In these preparations the oval form was approximately 10 per cent less than in stained smears while the elongated cells were proportionately increased. Other varieties showed less variation. (See Chart II) The figures are based on daily counts of one thousand cells made over a period of a week, using the same prep-

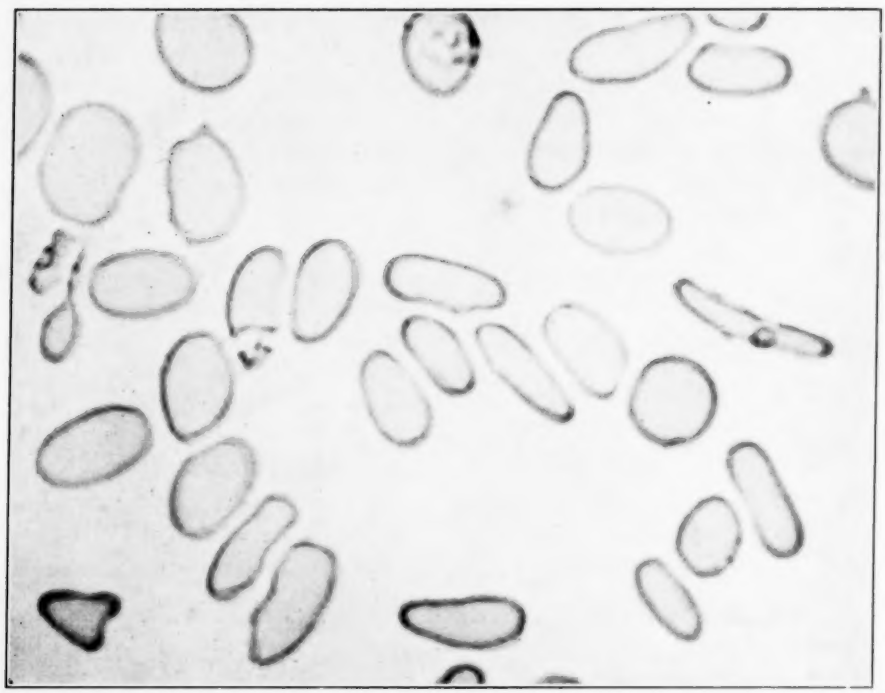

FIG. 1. High power microphotograph from sealed fresh preparation of blood of Adriana N. In this field elliptical shaped erythrocytes predominate.

aration and as nearly as possible the same portions of the slide. The lack of any appreciable morphological change definitely ruled out the possibility of sickle cell anemia. At times the long filamentous processes were seen to break off and move about freely in the serum. The abnormality of the corpuscles persisted in specimens washed in physiological salt solution and replaced in the patient's serum or that from normal individuals. It also persisted in cells in physiological saline. Her serum produced no deformity in the erythrocytes of normal persons. Phagocytosis of red blood cells was not observed in fresh specimens and was seen only twice in stained smears. At an incubator temperature of 54° C. all erythrocytes in fresh preparations assumed the discoid form within thirty minutes.

On two occasions the fragility test showed hemolysis beginning at 0.45 and complete at 0.36. Both the qualitative and quantitative van den Bergh tests have been repeatedly negative. Blood cultures have failed to show a growth of bacteria. Further details of the blood findings will be found in Chart III.

### TREATMENT

When first seen by us on October 3, 1927, the patient was weak and definitely anemic. Treatment was begun on October 10th. The good results obtained by Larsell and others (16) in

FIG. 2. Another field from the same slide as Figure 1. In this area elongated erythrocytes are particularly numerous At "A" is a corpuscle showing a long filamentous process. "B" is an unsually irregular poikilocyte.

(16) Larsell, Olof., Jones, N. W., Phillips, B. I., and Nokes, H. T., The Hematopoietic Effect of Nuclear Extractives in Anemia. J. A. M. A. 90: 75, (Jan. 14) 1928.

the treatment of anemias with the nuclear extractives of liver made us anxious to try this form of therapy, especially when we found that liver had not been used in the treatment of any of the reported cases of such blood disturbances. The nuclear extractives prepared in Dr. Larsell's laboratory are put up in 0.5 gm. capsules, six of which represent the nuclear material from one-half pound of liver. From the beginning the patient has taken, except for rest periods of a week or two, two capsules t.i.d. The results, while not as striking as in secondary anemias, have been encouraging. The hemoglobin has increased from 62 to 80 per cent and the erythrocyte count from 3,750,000 to 4,560,000. Subjective improvement has been out of all proportion to that in the blood picture. While under treatment the patient has carried on her household and nursing duties, gained 12 pounds in weight, and at present (April, 1928) feels stronger than she has for years. As the anemia decreased the gastrointestinal symptoms entirely disappeared and have not recurred. The pallor of the skin and mucous membranes is much less marked than formerly.

Only brief mention need be made of the blood and physical examinations of the remaining members of the patient's family.

Chart I shows the incidence of the abnormality in the entire family group. It is rather remarkable that all members of the second generation exhibit varying degrees of the anomaly. The diagnosis was made by setting up sealed fresh preparations of the blood from each individual and examining the slides at intervals over a period of 4 days. The erythrocyte count and hemoglobin are lower (Chart IV) than might be expected at the altitude of Missoula (3223 feet). However, with the exception of Johanna S. and William Kl., none of the family have symptoms of anemia. All others appear strong and healthy. Because of the limited time at our disposal physical examination was not done. Discoloration of the sclerae was carefully looked for but was not observed. None of the family give a history of leg ulcer.

## Discussion

The abnormality of the erythrocytes in this family is obviously hereditary since it occurs in one parent, all of his children and three of his six grandchildren. The incidence is greater than in Huck and Bigalow's group in which only two out of fourteen persons distributed over four generations had abnormal erythrocytes. The present study confirms Huck's suspicion of hereditary transmission of this condition. In our family, however, both sexes transmitted the anomaly, whereas in Huck's group only females gave evidence of its presence. Bishop's and Huck's subjects enjoyed good health and their blood was normal in every respect except for the abnormality of the erythrocytes. In our family the red cell counts and hemoglobin figures are generally low in spite of the apparent good health of the subjects. The one member whom we had the opportunity of studying carefully had a distinct anemia without a demonstrable cause. The role of the erythrocytic anomaly as a cause of the anemia is problematical, but the low red cell count and hemoglobin shown by so many of the group who were in apparent good health suggests the possibility of some hematopoietic disturbance.

A striking similarity exists between case L. B. S., described by Lawrence, and our patient, Mrs. A. N. His description and microphotographs of the blood are almost identical with the findings in our patient. His patient also had a secondary anemia but with more obvious causes than ours.

During the course of the study we were fortunate enough to observe an instance of the sickling tendency in a negro who was also suffering from multiple myeloma. A comparative study of the blood of the white and colored patients leaves no doubt that a difference exists between them. The erythrocytes of the negro sickled in the manner described and illustrated by everyone who has written on the subject of sickle cell anemia, while in the white patient the long spine-like processes at the ends of the cells were either lacking, or when present were blunted or rounded. In the gas chamber of Hahn and Gillespie (17) the

CHART I

OCCURRENCE OF ELLIPTICAL CELLS IN THREE GENERATIONS OF A WHITE FAMILY

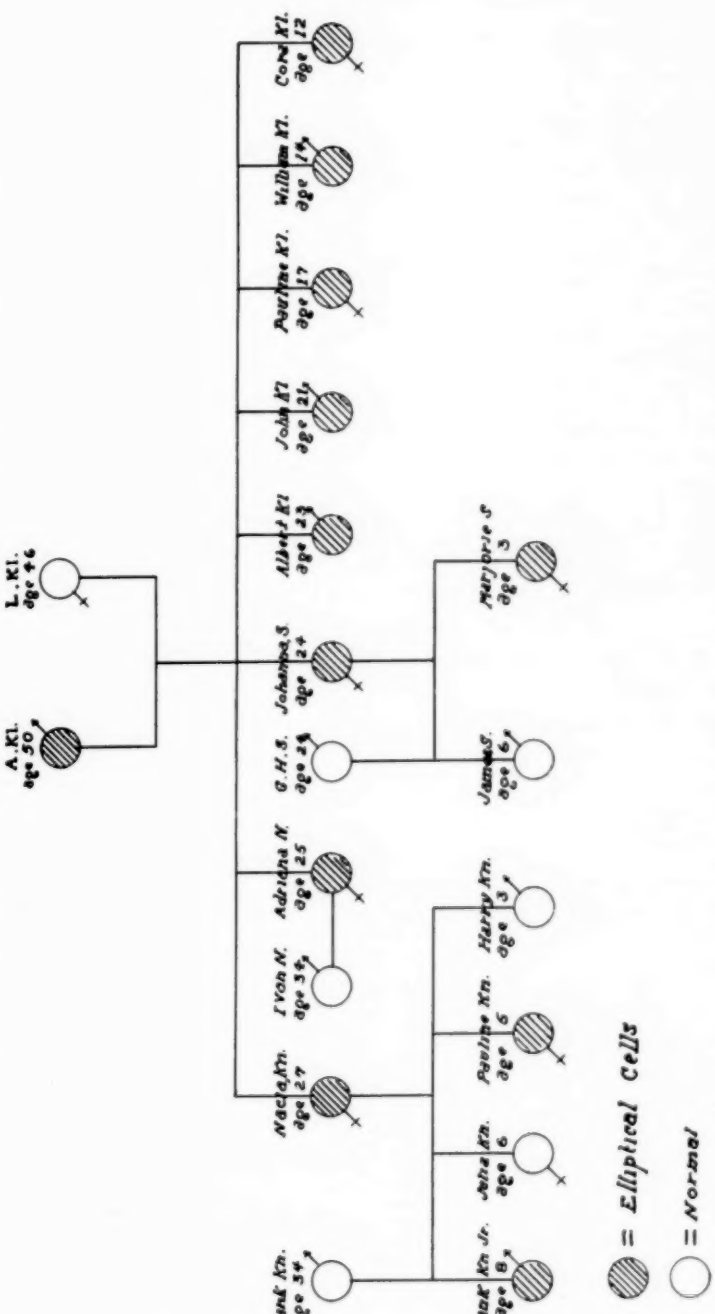

CHART II

| Shape of corpuscles | Stained smears | Fresh Preparations | Average dimensions of cells |
|---|---|---|---|
| Round | 6.7% | 2.4—11% | 9 μ. |
| Oval | 84.0% | 72.1—76.8% | 7 x 11 μ. |
| Elongated | 5.8% | 10.0—21.2% | 4.8 x 13.4 μ. |
| Processed (irregular) | 4.5% | 4.9— 7.3% | Variability too great to give average figures |

Types of erythrocytes occurring in the blood of Adriana N.

(17) Hahn, E. Vernon, and Gillespie, Elizabeth B., Sickle Cell Anemia. Report of a Case Greatly Improved by Splenectomy. Experimental Study of Sickle Cell Formation. Arch. Int. Med. 39: 233, (Feb.) 1927.

negro's erythrocytes sickled rapidly under the influence of carbon dioxide gas and reassumed the discoid form when oxygen was passed into the chamber. Such a change was lacking in the blood of the white patient. On passing carbon dioxide into the chamber a few cells became bilobed but nothing further developed.

The condition is apparently identical with the elliptical cell anomaly in negroes and whites described by Dresbach, Bishop and Huck and Bigalow. We are in full agreement with Huck and Bigalow that this condition may be differentiated from sickle cell anemia by the fact that the corpuscles are abnormal in outline on immediate examination and do not require a time interval for development as in sickle cell anemia. Careful counts over a period of several days have failed to disclose any appreciable change in the form or number of abnormal erythrocytes.

## SUMMARY

1. A rare familial and hereditary abnormality of the red blood cells occurring in members of three generations of a white family is described.
2. The abnormality is characterized by the presence of elliptical, elongated and irregular shaped erythrocytes present in the circulating blood of the affected individuals. In sealed fresh preparations of the blood no time interval is required for the development of the abnormal forms nor do these increase in number or show alteration in shape on standing as occurs in sickle cell anemia.
3. In contrast with two previously reported studies of this kind several of our subjects were more or less anemic.
4. One member of the family having well marked anemia and treated exclusively with the nuclear extractives of liver has shown an appreciable improvement in the hematological and clinical picture.

CHART III
(Adriana N.)

| Date | 10/6/27 | 10/10/27 | 10/23/27 | 11/12/27 | 12/12/27 | 1/6/28 | 2/22/28 | 3/22/28 |
|---|---|---|---|---|---|---|---|---|
| Hb (Sahli) | 62% | 63% | 65% | 71% | 76% | 79% | 68% | 86% |
| R.B.C. | 3,750,000 | 3,850,000 | 3,936,000 | 4,016,000 | 4,350,000 | 4,480,000 | 3,500,000 | 4,560,000 |
| C. I. | 0.8 | 0.79 | 0.76 | 0.85 | 0.83 | 0.86 | 0.94 | 0.86 |
| Anisocytosis | Moderate | Moderate | Moderate | Moderate | Slight | Slight | Moderate | Slight |
| Poikilocytosis | Marked | Marked | Marked | Marked | Marked | Marked | Marked | Marked |
| Nuc. R.B.C. | 1 Normoblast | 1 Normoblast | 1 Normoblast | none | none | none | none | none |
| W.B.C. | .... | 9,400 | 5,600 | 8,400 | 14,400 | 11,400 | 5,100 | 8,400 |
| P.M.N. | 78% | 62% | 69% | 66% | 76% | .... | 67% | 72% |
| P.M.E. | 1% | 1% | 0% | 0% | 2% | .... | 0% | 1% |
| P.M.B. | 0% | 0% | 0% | 0% | 0% | .... | 0% | 0% |
| L. Lymphs | 2% | 1% | 2% | 3% | 2% | .... | 2% | 1% |
| S. Lymphs | 16% | 36% | 29% | 30% | 20% | .... | 26% | 24% |
| Other W.B.C. | none | none | none | none | none | .... | none | none |
| Trans. | 3% | 5% | 0% | 1% | 0% | .... | 5% | 2% |
| Remarks | Before treatment | Treatment started | Under treatment | Under treatment | Under treatment | Under treatment | Menorrhagia | Under treatment |

CHART IV

| Name | Sex | Age | Date | R.B.C. | Hb. Sahli | Abnormal R.B.C. | Leukocytes |
|---|---|---|---|---|---|---|---|
| A. Kl. | M | 50 | 10/30/27 | 4,118,000 | 96% | Many rod, oat and sickle-like forms | 6,840 |
| Mrs. L. Kl. | F | 46 | 10/30/27 | 5,544,000 | 108% | none | 9,200 |
| Nacia Kn. | F | 27 | 10/30/27 | 3,760,000 | 84% | Few rod and sickle-like cells | 8,860 |
| Johanna S. | F | 24 | 10/30/27 | 3,304,000 | 85% | " " | 7,700 |
| Albert Kl. | M | 23 | 10/30/27 | 4,280,000 | 94% | " " | 6,620 |
| John Kl. | M | 21 | 10/30/27 | 4,224,000 | 84% | " " | 10,400 |
| Pauline Kl. | F | 17 | 10/30/27 | 2,936,000 | 79% | Many elongated, pear-shaped and sickle cells | 8,800 |
| William Kl. | M | 14 | 10/30/27 | 3,056,000 | 74% | " " | 7,900 |
| Cora Kl. | F | 2 | 10/30/27 | 3,320,000 | 83% | " " | 11,600 |
| Frank Kn. Jr. | M | 8 | 10/31/27 | 3,900,000 | 85% | Few elliptical and rod forms | 9,700 |
| Julia Kn. | F | 6 | 10/31/27 | ..... | .... | none | .... |
| Pauline Kn. | F | 5 | 10/31/27 | 4,600,000 | 86% | Very few oval and rod-like cells | .... |
| Harry Kn. | M | 3 | 10/31/27 | ..... | .... | none | .... |
| James S. | M | 6 | 10/31/27 | ..... | .... | none | .... |
| Marjorie S. | F | 3 | 10/31/27 | 4,640,000 | 96% | Few oval cells | 15,200 |

# Potassium Permanganate in the Treatment of Pneumonia

By John L. Chester, *Detroit, Mich.*

THE potassium permanganate treatment of certain diseases of toxic and infectious origin first came to my attention in a purely accidental manner. A professional colleague inadvertently mentioned that this oxidizing antiseptic and deodorant, held in aqueous solution and slowly injected into the rectum as a retained enema, had been reported from England as productive of startling results in pneumonia. I do not know that I gave much heed to the reported discovery at the time, if such a discovery there was. Like most practitioners I had become somewhat immune to enthusiasm over 'discoveries' of pneumonia specifics. Too many of them had been all too frankly disappointing. At any rate, I was then unfamiliar with the available literature on the subject, although conscious of the potency of potassii permanganas salt as an antidote in certain cases of poisoning.

In the early part of 1928, at Providence Hospital, I was called in consultation on an advanced and seemingly hopeless case of flu-pneumonia, which was later suggested by x-ray examination to be of tuberculous origin. The patient, a highly cultured gentleman of middle age, had been under treatment for six days, and was then in a pneumonia jacket and practically moribund. He was verging on extremis, and was markedly cyanosed, moaned considerably, coughed with great difficulty, and at intervals expectorated quantities of rusty colored sputum. There was a weak, thready pulse, abdominal distension, and bubbling, coarse râles heard in apices. The temperature was 102.2; pulse rate 115; respiration 40.

All known methods of treatment semed to have been used in this case, without producing a scintilla of evidence on which to base a favorable prognosis. The moment had arrived for heroic measures. It occurred to us that, whatever the merits of the now-recalled potassium permanganate treatment, it might justifiably be attempted here as a last resort.

## History of the Treatment

Hurried search of The Practical Medical Series (General Medicine), of 1927, while revealing somewhat meager confirmatory evidence, instanced (The British Medical Journal of March 7th, 1925) interesting experiments made under the direction of a general practitioner in the North of England. Dr. Herbert W. Nott, of Birkenhead, therein reported a series

of cases of toxic origin, which had shown gratifying improvement after being treated with a standard solution of this agent, single and in conjunction with thyroid extracts.

In March, 1924, the first case of pneumonia had been successfully treated by this method. A youth, aged 16½ years, a moderately severe case, with extensive involvement of the left lung, received half a pint of the standard solution twice daily for eight days. In a matter of hours the temperature was reported to have dropped two degrees F., expectoration was being coughed up more readily and rapidly lessened, and a greater degree of relief progressively experienced. The temperature had become normal in thirty-six hours. Convalescence eventuating, it was reported more rapid and less exhaustive than is usually observed under similar conditions treated by more orthodox methods.

Another English practitioner, Dr. Nelson J. Roche of Southsea, cognizant of and impressed with Dr. Nott's original experiments, had embraced the opportunity, in a measles epidemic in his immediate neighborhood, to test the value of this method of treatment. The results of the exposition of the solution at his hands are to be noted in The British Medical Journal of March 12th, 1927

Selecting five juvenile cases, complicated with well developed signs of broncho and lobar pneumonia, Dr. Roche's procedure, also using the standard solution, was approximately as follows: he gave 3 ounces every 3 hours for the first 12 hours; 3 ounces every 4 hours during the next 24 hours; 3 ounces every 6 hours for the following 3 days; 3 ounces every 12 hours for the final 4 days. Improvement was invariably noted within 24 hours, and in 48 hours, the changes were remarkably progressive. Respiration and pulse rate immediately slowed, temperature fell, restlessness abated, color improved, sleep became normal, cough became less frequent, and the patients were able to raise expectoration with comfort and ease, the sputum rapidly losing its rusty color. Within 6 to 8 days, Dr. Roche's cases assumed normal proportions symptomically, convalescence being rapid and uneventful in every instance.

### Our First Case

These English cases suggested that this single agent might have a true specific action on the micro-organisms of pneumonia as exemplified in our case, and we decided to put the treatment to the question. We used the standard solution,—two grains of permanganate to one and one-half pints of warm sterile water, injected rectally by means of a funnel and catheter, the patient lying on his left side, and with the intention of the fluid being retained.

The initial injection was 4 ounces, repeated every 3 hours. Within 12 hours the patient began to show some signs of improvement in a dropping of temperature, pulse rate, and respiration. He began to expectorate more freely, and in greater amount; he showed signs of emerging from his semi-comatose condition; he perspired freely, and began to take some interest in his surroundings. In 24 hours, the

temperature had dropped from 102.2 to 100, pulse rate from 115 to 88, with corresponding slowing in respiration from 40 to 26. The clinical picture at the end of the 48 hour period was equally progressive; temperature having fallen to 99, respiration being 32, and pulse rate 100.

Sleep was now being enjoyed for longer periods, the cyanosis was lessening, and the patient had the looks and expressed the feelings of all-round improvement. Voiding had been frequent in the meantime, although a still distended abdomen explained tardy bowel movement, which latter was satisfactorily relieved by an enema and one ampule of pituitary extract.

We maintained the potassium permanganate treatment in this case for ten days, the only deviation from the original routine being that, immediately on observing a normal chart,—in about four days after initiation of the treatment,—injections of 4 ounces of the solution every 12 hours were substituted for the 3-hourly injections. About the sixth day, there was a slight relapse, characterized by a chill, a rise in temperature, and an irregular pulse rate. The situation looked unfavorable for about twelve hours, but responded satisfactorily to medication.

Convalescence was then uneventful, and with more celerity and less fatiguing effort than is customary in a severe attack such as this was. The patient was discharged a month later, and eventually went to California to recuperate. On his return he was particular to report with the glad tidings that he felt absolutely no distressing after effects.

## Further Cases

Such was my satisfaction with the results of the first case handled in this manner, that I had no hesitation in thereafter using the potassium permanganate solution in every possible case where I considered it indicated. The following cases, treated with the standard solution at Providence Hospital, and observed personally or reported upon by others, go further to substantiate belief in this remedy in well defined pneumonia conditions:

*Case No.* 1812. W. C. Male, aged 31. Lobar pneumonia. Very toxic when first seen—T. 104.1, P. 140, R. 48. 5 ounces every 3 hours for 36 hours given. In 48 hours—T. 98.2, P. 80, R. 22. 3 oz. every 4 hours given for 2 days, then discontinued. Progress and convalescence uneventful. Discharged in good condition 9 days after admission.

*Case No.* 2013. H. G. Female, aged 10. Lobar pneumonia. In great distress when first seen—T. 104.4, P. 126, R. 24. 3 oz. every 5 hours for 48 hours ordered. At end of 48 hours—T. 103, P. 103, R. 28. Permanganate treatment discontinued at this point account of difficulty in retaining. Patient went on to a difficult recovery after having been operated on for an empyema which had developed. Left hospital in fairly good condition in about 30 days after admission.

*Case No.* 2337. L. D. Female, aged 45. Lobar pneumonia. Given 5 oz. every 3 hours for 48 hours, and thereafter continued until chart normal. Readings as follows:—T. 103.2, P. 140, R. 40. In 24 hours—T. 102, P. 120, R. 38. In 48 hours—T. 101.4, P. 120, R. 32. In 72 hours—T. 100.3, P. 109, R. 30. In 96 hours—T. 98.2, P. 88, R. 26. Recovery was uneventful. Patient was discharged in good condition after 10 days' stay in hospital.

*Case No.* 2634. B. G. Female, aged 31. Lobar pneumonia, mitral stenosis, and preg-

nant. Patient in great distress, and end seemed imminent in a few hours. X-ray (portable) confirmed diagnosis in right chest. Temp. 103.3, P. 118, R. 40. Given 5 oz. every 3 hours for 3 days, then reduced to twice daily. In 24 hours—T. 99.3, P. 80, R. 36. Progress continuing, discharge in good condition followed in 14 days after admission. This patient delivered a 6 months fetus on second day of treatment.

*Case No.* 901. J. P. Female, aged 29. Lobar pneumonia. T. 103.2, P. 110, R. 38. Given 4 oz. every 3 hours for 48 hours. Results at end of 24 hours—T. 100, P. 100, R. 35. Showed great improvement at end of 48 hour period, was sleeping well, signs having abated gradually. T. became normal in 4 days, P. staying around 80-90, with R. around 25-28. Went home in ambulance after 10 days, in fairly good condition.

*Case No.* 1839. K. W. Female, aged 57. Lobar pneumonia. T. 103, P. 130, R. 32. Chart readings:—In 24 hours—T. 102.5, P. 140, R. 36. In 48 hours—T. 98, P. 120, R. 30. 3 oz. every 3 hours for 3 days had been given. A relapse had occurred at the end of 48 hour period—T. going up to 102.5, P. 125, R. 35. This responded to medication, chart becoming normal and so remaining. Patient improved so that she was able to leave hospital by wheel chair in 13 days after admission. In fairly good condition.

*Case No.* 2069. Young child. Male. Lobar pneumonia. Very ill and very toxic. When first seen—T. 106, P. 148, R. 45. Given 1 oz. every 3 hours. Retention difficult, but was persevered with and eventually controlled relapses. Chart readings as follows: At end of 24 hours—T. 102, P. 120, R. 30. At end of 48 hours—T. 104, P. 110, R. 30. At end of 3rd day—T. 102, P. 120, R. 30. At end of 4th day—T. 106, P. 150, R. 50. At end of 5th day—T. 101, P. 140, R. 42. At end of 6th day—T 98, P. 120, R. 32. T. remained normal thereafter. This boy was transferred to Home in fair condition 16 days after admission.

*Case No.* 2088. Young boy, aged 1 year. Lobar pneumonia. Very ill. T. 103.2. Was given 1 oz. every 3 hours for 36 hours, reducing T. one degree every day for 3 days. Although several relapses intervened, T. became normal in 7 days. Had difficulty in retaining solution. After 23 days was transferred to Home in fairly good condition.

Although excellent results have been observed in private cases of pneumonia treated in the home with potassium permanganate, their details may be withheld at this time, there being a sufficiency of well authenticated institutional cases. The following 14 cases were also treated at Providence Hospital, and are briefly commented upon. They comprise the remainder of the original experiments with the solution, since when its exposition has been further persevered with, and with equally satisfactory results:

| *Case History* | *Treatment and Progress Notes* |
|---|---|
| No. 2220. J. C. Male. Aged 30. Lobar Pneumonia. | Given 3 oz. every 3 hours for 8 days. T. 104, P. 120, R. 30. Chart showed gradual descending curve, being normal on 6th day. Discharged after 14 days in good condition. |
| No. 2226. P. L. Male. Aged 30. Lobar Pneumonia. | Given 5 oz. every 3 hours for 48 hours. T. 104, P. 120, R. 35. A perfectly descending curve immediately shown. Normal on 5th day. Discharged on 21st day in good condition. |

| *Case History* | *Treatment and Progress Notes* |
|---|---|
| No. 2630. G. C. Female.<br>Aged 33. Lobar Pneumonia. | Given 4 oz. every 3 hours for 48 hours, then reduced until normal. T. 102, P. 100, R. 32. Chart is a perfect picture of a rapidly descending curve. Normal in 3 days and so remained. Discharged after 15 days in good condition. |
| No. 2987. M. F. Male.<br>Aged 23. Lobar Pneumonia. | Given 5 oz. every 3 hours for 48 hours. T. 104.5, P. 130, R. 50. Responded well. Another perfectly descending curve. Normal in 3 days. Discharged after 13 days in good condition. |
| No. 3075. C. N. Male.<br>Aged 39. Lobar Pneumonia. | Given 3 oz. every 3 hours for 48 hours. T. 101, P. 105, R. 35. Good response, chart becoming normal in 36 hours, and so continued. Discharged after 14 days in good condition. |
| No. 3547. N. J. Male.<br>Aged 36 Lobar Pneumonia. | This patient made good progress under other treatment for 7 days, T. having been reduced to normal, P. and R. in proportion. Had a relapse—T. 103.2, P. 118, R. 40. Given 4 oz. every 3 hours for 48 hours. Reacted well, and chart became normal in 36 hours. Discharged in 19 days after entrance in good condition. |
| No. 3903. A. G. Male.<br>Aged 35. Lobar Pneumonia.<br>Acute Pharyngitis.<br>Alcoholism. | Patient delirious—T. 101, P. 120, R. 30. Given 4 oz. every 3 hours. Did not respond. T., P. and R. rose very rapidly. Died within 48 hours in delirium tremens. |
| No. 4301 C. T. Male.<br>Aged 38. Lobar Pneumonia. | Given 3 oz. every 4 hours—T. 103, P. 160, R. 30. In 24 hours—T. 99, P. 90, R. 25. Maintained curve fairly even for 5 days, then had a relapse, not retaining solution well. Normal curve in 2 days, and continued so. Discharged after 12 days in fair condition. |
| No. 4802. F. S. Male.<br>Aged 32. Lobar Pneumonia. | Given 4 oz. every 3 hours for 48 hours. T. 105, P. 135, R. 30. T. dropped 4 degrees in 24 hours. Normal on 7th day and so continued. Discharge in good condition in 9 days. |
| No. 4902. L. H. Female.<br>Aged 62. Lobar Pneumonia. | T. 104.2, P. 100, R. 30. Given 3 oz. every 3 hours for 6 days. Very good response, then slight relapse. Continued this way for 2 or 3 days. Pushed treatment. Normal chart on 8th day, and so continued. Discharged after 13 days in fair condition. |
| No. 5454. D. W. Male.<br>Aged 21. Lobar Pneumonia.<br>Pleurisy. | T. 104, P. 120, R. 40. Given 4 oz. every 4 hours for 6 days. In 6 hours T. dropped 4 degrees, then rose for 3 days. Chart normal on 5th day and so continued. Discharged after 12 days in good condition. |

| *Case History* | *Treatment and Progress Notes* |
|---|---|
| No. 5506. M. S. Female. Aged 47. Lobar Pneumonia. | T. 104, P. 120, R. 30. Given 3 oz. every 3 hours. Chart curve rose slightly for 12 hours, then dropped suddenly —T. 100, P. 90, R. 28. Almost immediately patient relapsed, chart now showing a rapidly ascending curve to —T. 106, P. 130, R. 40. Failed to respond, and died at end of 4 days. |
| No. 6692. J. M. Female. Aged 18. Lobar Pneumonia. | T. 103, P. 120, R. 45. Given 3 oz. every 3 hours for 4 days. Immediate response. In 6 hours—T. 99, P. 100, R. 30. Did not retain well and widely fluctuating chart until 7th day, when it became normal and so remained. Discharged after 13 days in fair condition. |
| No. 8230. B. J. P. Female. Aged 8. Bronchopneumonia. | T. 104, P. 150, R. 56. Given 2 oz. every 4 hours. Immediate response. In 12 hours chart read—T. 98, P. 95, R. 28, and so continued, except P. rose again to 130, immediately falling to 70. Quick and satisfactory recovery. Discharged in 4 days in very good condition. |

The Providence Hospital cases above reported number 23 in all—21 recoveries and 2 deaths.

### Treatment Under Adverse Conditions

Eloise Hospital, maintained by Wayne County Poor Commission, furnished opportunity for the exposition of the solution under a totally different set of conditions. Here is the refuge of the derelicts of a community, material of possibly the worst kind for obtaining favorable results. Twenty cases of pneumonia, all severe and all complicated, some with chronic heart conditions of long standing, and nearly all admitted chronic alcoholics, were selected at random. Ten of these cases were handled by other than the potassium permanganate method, and all died. The remaining ten received the standard solution of the drug, and the undernoted tabulation represents a very fair picture of the treatment and results—fifty per cent recoveries in well-nigh hopeless circumstances:

| *Case History* | *Treatment and Progress Notes* |
|---|---|
| No. ——. W. J. Male. Aged 50. Bronchopneumonia. | A moderately severe case T. 102.2, P. 110, R. 40. Given 8 oz. every 3 hours. Did not retain well. Gradual response. Chart normal in 10 days. Discharged in good condition after 34 days. |
| No. ——. J. L. Male. Aged 45. Lobar Pneumonia. | Given 8 oz. every 3 hours. T. 103.2, P. 130, R. 55. Very good response. T. dropped 3 degrees in 12 hours. Chart normal in 48 hours. Discharged in good condition after 23 days. |

| *Case History* | *Treatment and Progress Notes* |
|---|---|
| No. ——. F. B. Male.<br>Aged 34. Lobar Pneumonia. | T. 104, P. 100, R. 30. Given 8 oz. every 3 hours. T. dropped 3 degrees in 12 hours. Chart normal in 48 hours. Injections stopped after 4 days. Discharged in good condition after 23 days. |
| No. 27449. J. M. Male.<br>Aged 49. Bronchopneumonia. | T. 104.5, P. 100, R. 20. Given 8 oz. every 3 hours. T. dropped 4 degrees in 12 hours, then went up to 103.5. P. and R. continued to rise. No further response. Died in 2 days. Pneumonia complicated with myocarditis. |
| No. 31254. T. K. Male.<br>Aged 22. Lobar Pneumonia.<br>Alcoholism.<br>Narcotic Addict.<br>4 plus Kahn. | T. 105.2, P. 140, R. 38. Given 5 oz. every 3 hours. In 24 hours—T. 100, P. 110, R. 30. Did not respond after this. Chart continued to rise and fluctuate, and life prolonged for 30 days. Died of pneumonia and complications. |
| No. 31326. D. A. Male.<br>Aged 42. Lobar Pneumonia. | Very ill. T. 102.5, P. 140, R. 50. Given 5 oz. every 3 hours. Did not retain well, and response was poor. Became normal for 12 hours after 7th day. Had relapse, went into delirium, and died on 12th day—pneumonia and myocarditis. |
| No. 31823. J. K. Male.<br>Aged 35. Lobar Pneumonia.<br>Empyema. | Was very low on entrance. Given 7 oz. every 3 hours. Did not respond. Became very toxic and died within 24 hours—pneumonia and myocarditis. |
| No. 32595. J. S. Male.<br>Aged 28. Lobar Pneumonia.<br>Delirium Tremens from Alcohol. | Was in straight jacket during treatment T. rose to 106, P. 140, R. 50. Died in 10 days—pneumonia and alcoholism. |
| No. 32693 F. K. Male.<br>Aged 45. Lobar Pneumonia. | Was in delirium on admission. T. 103, P. 120, R. 45. Given 5 oz. every 3 hours. Responded well, Gradual improvement in chart; normal in 6 days and so remained. Discharged in 17 days in good condition. |
| No. ——. J. S. Male.<br>Aged 32. Lobar Pneumonia. | T. 104, P. 120, R. 30. Given 8 oz. every 3 hours. Did not retain well at first. Pushed solution. In 12 hours—T. 100, P. 90, R. 25. Chart fluctuated widely for 4 days, becoming normal on 7th day, and so remaining. Recovery uneventful. |

In order to arrive at a true appraisal of the value of the potassium permanganate treatment in the Eloise cases, it must be remembered that the patients were of the most indigent and homeless type. Excesses, undernourishment, and in most cases, long exposure to the elements, had reduced vitality and resistance to infection to a very low point. Gathered from the streets of the city, as public charges, they had come here to die. One hundred per cent mortality had been the rule under similar conditions and orthodox treatment in the past. We are confident that where death was

delayed, it was altogether because of the potassium permanganate. Where it happened quickly, the solution had come too late for any possible results. The recoveries were prompt, and in the nature of a surprise to the staff of the hospital.

### Possibilities in Other Diseases

Although my more intimate acquaintance with the solution has been practically confined to acute cases of pneumonia, I was at once struck with the possibilities of its extension to other diseases. I find that these are more than favorable, inasmuch as a great variety of conditions have been treated by this method and reported upon. Dr. Nott notes receipt of information from interested correspondents that it has proved beneficial in the following instances: — pneumococcal meningitis, cerebro-spinal meningitis, acute bacillus coli infection, acute rheumatoid arthritis, cardiac asthma and dropsy, angina pectoris, eclampsia, gout, diabetes, gastric ulcer, colitis, chorea, certain skin infections, and other composite cases. Indications were to the effect, however, that mixed infections were somewhat less responsive, and in most cases the termination was by lysis instead of crisis.

### Effects on Blood Pressure

In the course of the preliminary experimental work and during the early practice of this therapy in England, it began to be noticed that some detoxicating process was taking place in the blood as well as in the tissues, in cases recognized as of toxic origin. Confirmatory evidence began to accumulate that the solution had its influence on the blood pressure, and was often successful in lowering high tension. Dr. Nott has reported (The British Medical Journal, December 26, 1925) on a long list of such cases in the belief that, whatever they proved, they at least justified the recording of certain impressions which it was hoped would be found sufficiently interesting to stimulate further inquiry.

### Chemical Action

There are three stages in the reduction of potassium permanganate corresponding with the separation of 1, 3, and 5 atoms of oxygen per two molecules of salt. The decomposition products are, respectively, potassium manganate, manganese dioxide, and manganous salt. Two gram-molecules of potassium permanganate contain the equivalent of 80 grams of available oxygen, which is rapidly given off in the presence of water. The residuum, being manganese dioxide, is an antiseptic and an antidote for certain poisons. It is asserted to be the most efficient antidote to snake venom. What then are its effects on the toxins produced by pneumonia? Dr. Nott, again, is impressive in his attempt to forestall this anticipatory question. He says:

"Let it be remembered that the human toxins have long been known to resemble snake venoms; that snake venoms are of metabolic origin, and, numerous as they are in number, variety and potency, potassium permanganate is an antidote to all, or nearly all. A significant fact is that all venoms act on the animal body in one of two ways, and can be grouped under two physiological

headings. They are either hemotoxic or neurotoxic in their action, death occurring from changes in the blood or from paralysis. Now, if the human body is producing toxins resembling snake venom, is it not possible that we poison ourselves by our venoms affecting the blood and the nervous system? And if potassium permanganate in minute quantities is an antidote to snake venoms, why not also to the human venoms?"

### A Simple Therapy

The potassium permanganate treatment is inexpensive, easily understood, and admirably adapted for ordinary home nursing. Its very simplicity tends to detract attention from its potency and efficiency in certain grave toxic and infectious conditions, and this fact alone may have had something to do with its being so long overlooked by the profession as a remedy promising favorable results in pneumonia. One does unconsciously look for intricate technic in the employment of new remedies. In my experience with it, I have had occasion to comment on inattention and even reluctance on the part of some nurses caring for private cases in homes, during a course of treatment. I invariably attributed this to the fact that they were being called upon to handle as the chief weapon, something they had been accustomed to consider as a by-product, a minor aid and appurtenance to some other major remedy.

Simple and non-technical as the treatment is, yet, it has its inhibitions. The tablets or crystals should have no place on the shelves of the family medicine cabinet with the commoner domestic remedies, which can be and are used promiscuously for minor ailments. They should only be used under the physician's directions, and they must be pure. The tablets, which are freely soluble in water, are probably more reliable than the commercial crystals, and are therefore to be preferred in the preparation of the solution.

Injection by means of a funnel and catheter is given, with the patient lying on his left side, and must be made carefully and slowly, otherwise a spasm of the bowel will result, and entrance be denied. The ideal time for the injection is about half an hour after a bowel movement, when a cleansing enema might well be given, retention being more satisfactory when the solution is comfortably hot. The quantity and strength of the solution, and the length of time between injections, will vary according to the individual needs and circumstances of given cases. The factors of age, severity of attack, and capacity of retention, in turn will govern the procedure. Mucous casts of the bowels may be encountered during the progress of the treatment, and should be warned against and discounted.

Dr. Nott mentions the cachet method of administration—1/8 to 1/2 grain of the powdered drug enclosed in a small sized cachet, and swallowed with half a point of hot water. In cases where rectal injection is not practicable, I presume that this method would have its advantages, and I would welcome a verdict from interested observers on the subject. I see no reason why the solution could not, under proper instructions, be self-administered rectally in ambulatory cases, but

I would sound a note of warning against irresponsible and uninstructed treatment.

There is too great a possibility of inducing poisonous symptoms, to encourage the adoption of a "home remedy" attitude towards the treatment, and to allow the prescription to be handed around indiscriminately. By all means let the first injection be made under the personal supervision of a physician or capable nurse, and see to diminishing color, the disappearance of it that the others are made according to scientific directions. Then will this treatment be reassuring to the patient, then will the home properly join with the institution in furnishing the indisputable proofs as to whether principle or theory is to govern the decision:—is potassium permanganate a specific in pneumonia?

### Is It a Specific?

Witness the lung signs, cyanosis invariably present and ofttimes extreme, the high temperature, the quickening of respiration and pulse rate, the harsh, strained bark of a labored cough, and the rusty red sputum difficult of expectoration. Observe the restlessness, the fitful sleep, the lassitude that presages lack of interest in life or death, slowly developing into delirium, stupor, and sometimes complete unconsciousness. Pneumonia in its many manifestations!

Conceive the clinical picture being rapidly changed by this new therapy to an awakened interest in surroundings; a lowering in temperature and pulse rate, slower and deeper respirations,—all in a matter of a few hours. Observe, as I have done in many instances, the cyanosis disappearing, the rusty sputum coming up freely and in restlessness and sleeplessness, — in twenty-four hours. I have noted temperature, pulse rate and respiration become normal in from forty-eight to seventy-two hours after the first injection, and I have seen patients pronounced in good condition and fit to be discharged in a shorter time than I would have believed possible under any other regime.

The suggestion would be that potassium permanganate has all the earmarks of having a true specific action on the micro-organisms of pneumonia. Apart from the English cases I cannot find that a determined effort has been made to really test its efficiency. The very prevalence of an infection so virulent and intractable as this is should be sufficient to encourage widespread efforts to discover whether or not the hopes already engendered for the treatment are founded on good and sufficient premises.

The beforementioned experiments and treatments were made possible by hearty co-operation and assistance on the part of the following:—Doctors C. T. McClintic, J. Agins, E. J. Panzner, F. S. Porretta, E. C. Texter, C. P. Sibley, A. O. Brown, B. H. Priborsky, W. J. Seymour, E. H. Carroll, H. L. Perlis, L. J. Gariepy, H. F. Raynor, L. J. Bailey, J. M. Burgess, A. K. Northrop, J. N. Jaekel, Geo. A. Trizisky, Chas. A. Lilly, J. E. Bennett, D. U. Saunders, A. J. Hollander, H. Charney, W. Koester, F. E. Cameron.

# Total Base In Gastric Contents And Gastric Secretion*†

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STUDIES of the gastric juice have centered largely around the question of acidity and little attention has been paid to the base in the gastric secretion. Since Reaumur isolated the gastric juice and proved its solvent action on ingested food, gastric secretion has been the subject of extensive research. But Young's observation that the secretion is strongly acid, and Prout's that the acid is hydrochloric directed study to the acids with almost total indifference to the other constituents. It is only comparatively recently that anything has been done with regard to the determination of total chlorides. Inasmuch as the bases are concerned vitally in the secretion of acid and in its neutralization, they are in many respects as deserving of study as the hydrochloric acid.

There have been numerous hypotheses as to the mechanism of the production of hydrochloric acid in the stomach. Maly advanced the idea that it resulted from the interaction of two salts of sodium, sodium di-hydrogen phosphate and sodium chloride, $NaH_2PO_4 + NaCl \rightarrow HCL + Na_2H\ PO_4$.** He believed the reaction to be intracellular. Harvey and Bensley, and others, expressed the belief that the reaction which results in the formation of hydrochloric acid takes place in the foveola of the gland rather than in the cell. Collip, in 1912, by microchemic methods of precipitating phosphates, chlorides, and carbonates in the tissues of the gastric mucosa, demonstrated a definite change in the chemistry of the parietal cells and the intracellular tissue during rest and activity. During rest, chloride was present in abundance in the interstitial tissues, and phosphate and carbonate predominated in the parietal cells. During activity, the presence of all three radicals was demonstrated in the parietal cells. Since little potassium could be found, he assumed that most of the cation present was sodium.

Concerning the bases and their rôle

*The work was done under the supervision of Dr. Leonard G. Rowntree and is one of three studies. One of the two studies which will be published later is on the quantitative determination of gastric secretion by Dr. H. V. Dobson, and the other on the quantitative study of the different bases in the gastric juice by Dr. Theodore Bliss.

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**This reaction does not occur in vitro.

there is little accurate information. Boldyreff, in 1915, postulated the theory that the bases in the gastric juice were derived from regurgitation of alkaline fluids (bile, and pancreatic and intestinal juice) from the intestine, and that this was responsible for the automatic regulation of gastric acidity. Bell and MacAdam, Apperly and others have supported this theory.

### Method of Study

The present study was undertaken with the idea of determining: (1) the total base present in gastric secretion, (2) whether it is secreted as such by the gastric mucosa, and (3) the variations in total base during fasting, during the secretory phase, and in various pathologic states.

During the course of my work an article appeared by Gamble and McIvar on the fixed base in the gastric juice. However, they used a test-meal as a stimulus and reported a wide range of base in gastric secretion, whereas I used histamine. The patients under observation were from the gastro-enterologic service, and a dog, weighing 12 kg., with a Pavlov pouch was used as a control. Observations were also made on seven normal persons.

The reaction to histamine, administered subcutaneously, is preferable to the test-meal in the study of gastric secretion because extraneous material is not introduced into the stomach and, in calculating results, correction for dilution is not necessary. In the first twenty cases a dose of 0.25 mg. was used, but later 0.1 mg. was found to be sufficient to stimulate secretion and proved to be more satisfactory. This amount of histamine was found efficacious in the stimulation of secretion in some cases in which there was achlorhydria with the test-meal. The smaller dose is preferable because it results in a shorter secretory phase and permits the determination of change in secretion both at the beginning and at the end of the secretory phase. The smaller dose is also advantageous because it may be used without the disagreeable physiologic effects, such as reversed peristalsis with reflux of duodenal contents, and lowered blood pressure accompanied by headache and uncomfortable flushing, which are sometimes encountered when a larger amount of histamine is administered.

On the morning of the examination the subject to be tested was not given breakfast, and the contents of the stomach were aspirated and saved. Histamine was administered and subsequently aspirations were made every fifteen minutes. In the earlier tests, when the larger doses (0.25 mg.) of histamine were used, the specimens were taken at intervals of fifteen minutes, placed in one container, and a single analysis made. With the administration of smaller doses of histamine and the resultant shorter secretory phase, each aspirated specimen was examined separately. Total acid, free acid, chloride and total base in each specimen were determined. The presence of bile or mucus was noted and graded.

The dog that was used in the experiments was continuously in a healthy condition and served, I believe, as a normal control. Secretion from a Pavlov

pouch is pure gastric juice uncontaminated by saliva or duodenal contents. Because of the small size of the pouch it was necessary to prolong the secretory phase in order to obtain sufficient secretion for analysis. Doses of histamine of 0.1 to 0.5 mg. were used and the contents of the pouch were collected at intervals of an hour. Toward the end of the series of experiments, the opening of the pouch became smaller, and it was therefore possible to collect secretion in the morning before food was given comparable to the contents of the stomach collected in the morning from the patients studied.

The usual method of titration with 0.1 N sodium hydroxide was used for total and free acidity, phenolphthalein being an indicator for the former and dimethyl-amino-azobenzol for the latter. The determination of chlorides was carried out by the Volhard-Harvey method. The total base was determined by the method of Stadie and Ross, the only departure from the original procedure being in the removal of phosphates. According to their technic, phosphates are precipitated by the addition of an equivalent amount of 0.1 N ferric alum. This requires separate determination of phosphates. In working with the gastric juice, this is impractical because the occasional presence of bile interferes with the use of direct colorimetric methods of estimation, and the "wet ash" method is laborious and tedious. Gastric juice contains only small amounts of phosphate, so the process was simplified by the addition of 0.2 c.c. of 0.1 N ferric alum to precipitate the phosphate and the excess iron was removed by means of 4 N ammonium hydroxide. Acidity is expressed in the conventional way and base likewise as cubic centimeters of 0.1 N acid or base for each 100 c.c. of contents.

### Fasting Secretion From Seven Normal Persons

The contents of the stomach taken after fasting from seven normal persons (laboratory workers) were aspirated and examined for free hydrochloric acid, total base and bile. This was done in order to establish a normal for the content of the human stomach after fasting. Hydrochloric acid was present in only two instances in which it was 10 and 29 and the total base 92 and 90, respectively. In the other five subjects the total base was 101, 102, 102, 108 and 126, respectively. Objection has been raised to using the contents of the stomach after fasting because of the claim that it is largely swallowed saliva. In this connection it was interesting to find that the saliva of these persons averaged 52 c.c. while the average base for the contents of the fasting stomach group as a whole was 102 c.c. 0.1 N base for each 100 c.c.

### Gastric Secretion After Stimulation with Histamine

*Nine cases of normal hydrochloric acid content.*—In this group total acids varied from 35 to 56 c.c. of 0.1 N acid for each 100 c.c. and free acid from 10 to 40 c.c. The total base at the height of the secretory phase ranged from 82 to 86 c.c. 0.1 N except in one in-

TABLE 1
RESULTS OF ADMINISTRATION OF HISTAMINE IN SELECTED CASES

| | Fasting | | | | Fifteen minutes | | | | Thirty minutes | | | | Forty-five minutes | | | | One hour | | | | One hour and fifteen minutes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case | Total acid | Free acid | Total base | Chloride | Total acid | Free acid | Total base | Chloride | Total acid | Free acid | Total base | Chloride | Total acid | Free acid | Total base | Chloride | Total acid | Free acid | Total base | Chloride | Total acid | Total base | Chloride | Histamine, mg. | Comment |
| 1 | 40 | 22 | 82 | 78 | 56 | 40 | 68* | 72 | 56 | 40 | 68* | 72 | 56 | 40 | 68* | 72 | | | | | | | | 0.25 | Normal acids, neurosis |
| 2** | 6 | | 128 | | 6 | | 92 | | 26 | 16 | 82 | | 50 | 30 | | | | | | | | | | 0.1 | Normal acids, arthritis |
| 3*** | 56 | 30 | 84 | | 104 | 90 | 28 | | 92 | 88 | 34 | | 84 | 78 | 98 | | | | | | | | | 0.1 | Hyperacidity, gastric ulcer |
| 4 | 16 | | 90.5 | | 64 | 52 | 60.4 | | 90 | 74 | 50.6 | | 66 | 53 | 60.4 | | 70 | 52 | | | | | | 0.1 | Hyperacidity, arthritis |
| 5 | 4 | | 102 | 82 | 6 | | 92* | 78 | 6 | | 92* | 78 | 6 | | 92* | 78 | 8 | | 144** | 72 | 18 | 144 | 72 | 0.25 | Achlorhydria |
| 6 | 10 | | 76 | | 8 | | 86 | | 8 | | 86 | | 8 | | 86 | | 10 | | 106*** | | 10 | 106** | | 0.25 | Achlorhydria |
| 7 | 32 | 20 | 156 | 74 | 66 | 54 | 112 | 102 | 44 | 54 | 112 | 102 | 24 | 28 | 120 | 88 | | | | | | | | 0.1 | Gastro-enterostomy |
| 8 | 20 | 8 | 116 | 84 | 62 | 48 | 104 | 96 | 56 | 42 | 120 | | 52 | 30 | 136 | 88 | | | | | | | | 0.1 | Gastro-enterostomy |

*Fifteen, thirty and forty-five minute=specimens pooled.
**One hour and one hour and fifteen minute=specimens pooled.
***Bile was not present.

stance. In this case the base at the height of secretion was only 68 c.c. and curiously enough was in the patient with the highest acidity (56 total, 40 free).

The inverse relationship of acid and base is shown in Table 1. In Case 1 the free acid increased from 22 to 40 and the base decreased from 82 to 68. In Case 2 the free acid increased from 0 to 30 and the total base decreased from 128 to 82.

*Six cases of hyperacidity.*—In this group the total acids varied from 62 to 120 c.c. of 0.1 N acid and the free acid varied from 47 to 102 c.c. The total base varied from 28 to 85 c.c. 0.1 N for each 100 c.c. of contents. Two instances showing the inverse relationship are given (Cases 3 and 4, Table 1). Case 3 is one of gastric ulcer in which the free acid increased under stimulation by histamine from 30 c.c. of 0.1 N to 90, returning to 78, and the base decreased from 84 to 28 c.c., returning to 98 c.c. at the end of the period of forty-five minutes.

*Seven cases of benign achlorhydria.*—The concentration of total base in patients with benign achlorhydria was found to be higher than in normal persons or patients with hyperacidity. Administration of histamine was not followed by the appearance of hydrochloric acid in four of the six cases studied. It is extremely significant, however, that in these four cases increased secretion of total base resulted. The increase in concentration of total base, with failure to liberate hydrochloric acid, calls for further investigation. The effect of stimulation by histamine is given for Cases 5 and 6 (Table 1). In Case 5 the base after fasting was 102 c.c 0.1 N. At the end of an hour the base was 144 c.c. and free hydrochloric acid was not secreted. In Case 6 the base increased from 76 to 86 c.c. at the end of fifteen minutes and to 106 c.c. at the end of an hour and fifteen minutes. A trace of bile was present in each of these specimens, indicating regurgitation of duodenal contents.

*Nine cases of gastro-enterostomy.*—The concentration of base in this group was the highest found in any of the series. Free hydrochloric acid was present in all but one case, despite the fact that bile was present in every specimen. The inverse relationship of concentrations of acid and base is shown in Cases 7 and 8 (Table 1). In Case 7, the free acid increased from 20 to 54 c.c. of 0.1 N acid and the base decreased from 156 to 112 c.c. 0.1 N and later rose to 120. In Case 8, the free acid increased from 8 to 48 c.c. and the base decreased from 116 to 104 and later rose to 136.

*Results in the dog (eight experiments).*—In the juice of the dog after fasting the free acids varied from 0 to 12 c.c. of 0.1 N for each 100 c.c. The total acid was likewise low, varying from 10 to 16 c.c. of 0.1 N acid. On the other hand, the bases were very high, ranging from 115 to 150 c.c. N. Following the administration of histamine, as the secretion of acid increased, invariably the concentration of the base decreased, while later with the decline of the secretory phase the free

***Bile was not present.

acid decreased and the base increased in concentration and approached its former level (Fig. 1). The most striking results are seen in Experiments 1, 2 and 3 (Table 2). In these experiments, the total acid reached 120, 140 and 108 c.c. of 0.1 N for each 100 c.c., respectively, two hours after the administration of histamine. The free acid reached 80, 130, and 92 c.c., while the base, which was well above 100 in the contents on fasting in each instance, had decreased to 23, 7.4 and 60 respectively. The similarity of response in the dog and in patients is shown in Figure 2.

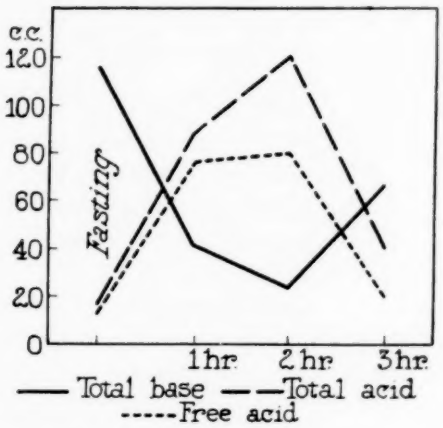


FIG. 1. Secretion from dog. Reciprocal relationship of acid and base during the entire secretory phase. (The ordinate represents cubic centimeters of 0.1 N acid and base for each 100 c.c. of solution.)

TABLE 2
GASTRIC SECRETION OF THE DOG

| | Experiment 1 | | | Experiment 2 | | | Experiment 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total acid* | Free acid* | Base, total** | Total acid* | Free acid* | Base, total** | Total acid* | Free acid* | Base, total** |
| Fasting | 16 | 12 | 115 | 10 | | 134 | | | 150 |
| First hour | 88 | 76 | 42 | 110 | 90 | 33 | 98 | 68 | 68 |
| Second hour | 120 | 80 | 23 | 140 | 130 | 7.4 | 108 | 92 | 60 |
| Third hour | 40 | 20 | 65 | | Amount not sufficient | | 100 | 80 | 65 |

*Acid expressed as 0.1 N acid for each 100 c.c of solution.
**Base expressed as 0.1 N base for each c.c. of solution.

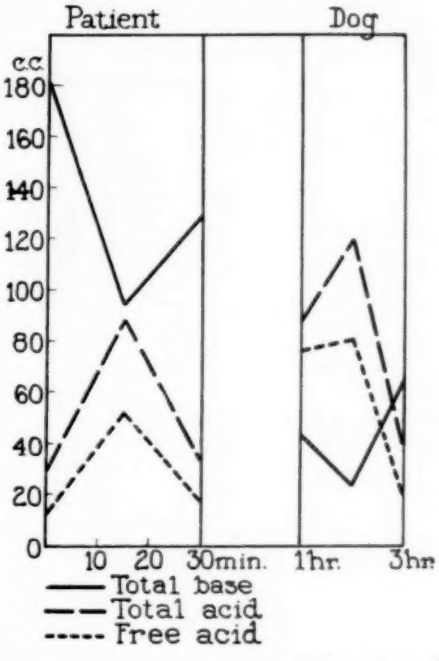


FIG. 2. Data charted together to show the similarity of reaction during the secretory phase. (The ordinate represents cubic centimeters of 0.1 N acid and base for each 100 c.c. of solution.)

*Variation in the curve of the chloride.*—The curve of the total chloride during the secretory phase varied with the curve of the acid. The total chloride tended to increase in concentration during the secretory phase. The bound or base chloride was calculated by subtracting the total acid from the chloride. (8) The base chloride was higher in the contents of the stomach on fasting than at the height of the secretory phase. It would seem that during secretion the base chloride has been largely converted into hydrochloric acid. The base chloride in hyperchlorhydria was found to be extremely small in amount, whereas in hypochlorhydria it was present in large amounts (Fig. 3).

*Phosphate content of the gastric secretion.*—Quantitative estimations of the phosphate in the gastric secretion were made in a few cases and also in the secretion from the dog. The phosphates did not show significant variation during the secretory phase.

## COMMENT

The most significant observations in relation to the total base in the various groups of cases are shown in Table 3. From this it will be seen that the lowest concentration of total base in the gastric juice is found in patients with hyperacidity, and the highest in patients with achlorhydria, and particularly in patients who have been sub-

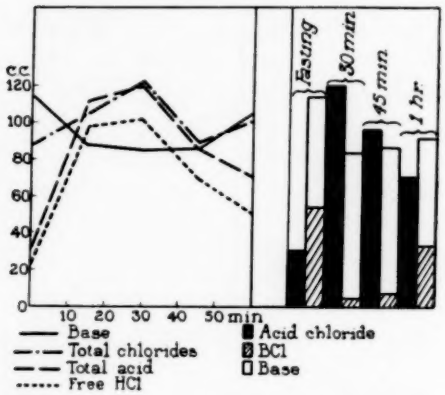


FIG. 3. Typical relationship of acid and base. The chloride curve follows directionally that of the acid but this base chloride diminishes during secretion.

TABLE 3

THE AVERAGE TOTAL BASE DURING THE FASTING STAGE AND SECRETORY PHASE FOR ALL CASES

| | Cases | Fasting, c.c. 0.1 N. for each 100 c.c | At height of secretion, c.c. 0.1 N. for each 100 c.c. |
|---|---|---|---|
| Normal hydrochloric acid 10-40 | 9 | 91.2 | 63 |
| Hyperacidity, free hydrochloric acid above 40 | 6 | 105.8 | 81.8 |
| Benign achlorhydria | 7 | 113.3 | 90 |
| Gastro-enterostomy with free hydrochloric acid | 8 | 134 | 97 |
| Gastro-enterostomy without free hydrochloric acid | 1 | 142 | 142 |

jected to gastro-enterostomy. This is true for secretion during fasting and for the secretion after stimulation by histamine. The curve for secretion of the total base following the use of histamine is in inverse relationship with the curve of the total and free acid. This is true for normal persons and the normal dog, and is also evident in the various pathologic conditions studied. As a rule, stimulation by histamine results in increased secretion of acid and diminution in the secretion of the total base. In benign achlorhydria in several instances, however, histamine has resulted in increased secretion of base.

Gastric juice normally contains considerable amounts of base. During the secretory phase, the total base varies simultaneously with the secretion of acid, but in the opposite direction, thus exhibiting an inverse relationship. Gastric secretion involves changes in the concentration of both acid and base. The study of the bases in gastric secretion is as worthy of consideration as is that of the acids.

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# Postinfluenzal Vomiting With Symptoms Of Lethargic Encephalitis

By Albert S. Welch, A.B., M.D., *Clinical Instructor in Medicine, University of Kansas School of Medicine, Kansas City, Missouri*

DURING the past few months, in a practice consisting chiefly of diseases with prominent symptoms referable to the alimentary tract, there have come to attention several unusual cases in which the chief complaint was vomiting; and examinations failed to yield data upon which they could be classified in any of the well-known groups of conditions in which vomiting is an outstanding symptom. A cursory investigation among other members of the medical profession of this city brought to light a few similar cases, diagnosed doubtfully as "neurotic vomiting" "nervous indigestion" or "food poisoning." In each instance, the physician could not recollect with certainty having encountered such cases during the six preceding years.

In all of these cases there were some of the symptoms found in epidemic encephalitis, and in none were there symptoms incompatible with that diagnosis. In view of the present wide-spread epidemic which bears so many features in common with the epidemic of "influenza" of 1918, and the fact that neurologists are again finding cases of *advanced* lethargic encephalitis of the influenzal type, it seems probable that the cases herewith reported represent a condition of *mild epidemic* (*lethargic*) encephalitis (sleeping sickness).

A report of this nature is made at this time because in spite of the voluminous literature on epidemic encephalitis, little note is taken of early cases except from a neurological point of view; and the striking symptoms mentioned below suggest instead disease of the gastro-intestinal tract.

Von Economo, in the first paper to attract much attention, his original article (1) written under the stress

(1) Economo, C. von: Encephalitis lethargica, Wien. Klin. Wochschr. 30, No. 19: 581, May 10, 1917.

of war times, described only advanced or outstanding examples of this disease. But Hall (2) described a case

(2) Hall, Arthur J.: Epidemic Encephalitis, Wm. Wood and Co., 1924, P. 5.

among his records of 1903 with cardinal symptoms of malaise, somnolence, incoordination of eye movements, nausea, vomiting and fever, of one week's duration. This patient gradually improved and went on to complete recovery except for twitching of the face that persisted even after several years.

The three commonest symptoms of epidemic encephalitis are malaise, lethargy and ophthalmoplegia. In *acute* epidemic encephalitis that has advanced to the stage of obvious seriousness, the mortality is as high as 40 per cent; yet many of these cases do apparently make good recoveries. As the years pass, however, it is being recognized that *residua*, often inconspicuously slight, remain in a large proportion of these individuals. The *chronic* cases that have advanced to the stage of paralysis agitans of course are more apt to remain badly affected.

The cases herewith reported are believed to be examples of *mild acute epidemic encephalitis*.

*Case* 1.—An active chemico-mechanical engineer, twenty-five years old, had enjoyed good health, worked hard, and slept about seven hours each night for many years. The members of his family all had "flu" in the fall, but he was the least affected and never lost a day of work. However, from that time on, he felt tired and finally suffered with *malaise* so extreme that the least effort made him feel "all in". He had to force himself to get up in the morning. He had no energy to carry on his work at the office, and by noon his legs felt so "wobbly" that he had to go home and rest.

*The thing that brought him to the doctor was nausea and vomiting.* He felt nauseated continuously and vomited as often as six times a day. This had gone on for a week. He described his sensation as that of being seasick. He thought he had "nervous indigestion," and a pathologist had told him that he was vomiting because his wife was pregnant.

The vomiting had started rather suddenly, and he vomited before breakfast but never brought up food eaten the evening before. He seldom brought up more than a third of a cupful of colorless, slightly bitter fluid.

He absolutely denied pain of any kind and had no headache. He passed formed stools daily without using cathartics. He said he would have been hungry were it not for the nausea, yet he ate his meals and had lost only five pounds during the four weeks of his illness.

He was dizzy most of the time, but did not display any tendency to fall to one side or the other. He admitted that his dizziness was quite troublesome and was apparently a part of the "seasickness" of which he complained.

When questioned in regard to his habits, he gave a surprising story of recent *somnolence*. Since his present illness began, he felt sleepy all of the time—would sleep soundly twelve hours at night, take a long nap in the afternoon, and in the evening while a noisy party was going on at his house he would lie down on the davenport and sleep soundly "for two and a half hours, until the dishes were all washed and the guests were going home."

He denied double vision.

He denied numbness, unilateral weakness, symptoms referable to the special senses and to the central nervous system except as mentioned above.

He denied symptoms referable to the nose and throat, the trachea and lungs, the circulatory system, the urinary and genital system, and the joints. He denied "hives" and other symptoms referable to the skin.

He smoked twenty cigarettes a day, and had been doing this for several years; but his symptoms persisted after he had stopped smoking for a week.

Three months earlier, he had been worried about one of his employees, but the difficulty was settled, and he denied worrying about anything since his recent illness began.

He denied being near the fumes of poisonous chemicals.

He had never suffered any similar previous illness.

Examination failed to reveal any focus of infection of the upper respiratory tract. The tonsils had been removed. The sinuses seemed to be in good condition, and X-ray plates failed to reveal dental caries.

There was slight drooping of the eyelids but no evidence of muscle palsy, no irregularity of the pupils, and no noteworthy alteration in the eyegrounds. Tests failed to detect labyrinth disorder, and reflexes from the turning test were slightly less than the average time.

Except for appearing weary, the patient's features were not changed and his skin was not oily. His blood pressure was 105/60, his pulse rate 70, and his *temperature 99 degrees.*

Nothing noteworthy was found upon examination of the chest. The abdomen was flaccid and peristaltic sounds were normal. The kidneys were not palpable.

Abdominal reflexes were brisk and equal. The knee-jerks were weak, even when supplemented, but equal; so also were the triceps jerks. Babinski's sign was absent. Careful tests for sensory disturbances failed to show any departure from the normal.

Laboratory tests on the blood, urine and stool were essentially "negative" except for an *increased white cell count.* This varied between 10,000 and 12,300 when examined on several occasions, and the polymorphonuclear neutrophils made up approximately 75 per cent of this number. No parasites were found in warm fresh stools.

This patient presented symptoms characteristic of a low-grade toxemia, with vomiting of cerebral origin. The differential diagnosis included poisoning from chemicals at the shop, poisoning from excessive use of tobacco, focal infection of the upper respiratory passages, lungs or gallbladder, and cerebral disturbances on a basis of worry or nervous exhaustion. None of these were satisfactory. The diagnosis finally made was low-grade encephalitis, and the subsequent course of the case seemed to substantiate this impression.

Over a period of months, he slowly but steadily improved. The vomiting stopped after ten days, but the malaise, vertigo and somnolence continued. After five weeks, the vertigo was gone. After seven weeks, the somnolence had changed to insomnia, but two weeks later he was again drowsy. After nine weeks he felt good except for slight malaise. He had gained five pounds, had a temperature under 98.8 degrees and a leucocyte count of 8,000. But during the tenth week he developed a right-sided headache, and the *right pupil became larger than the left.* He said he again found an occasional temperature of 99.5 degrees, but no fever was noted upon occasional trips to the office.

*Case* 2.—A man forty-five years old had the "flu", but was the least affected of any member of his family. He grew more and more tired thereafter, found he could not read as well as formerly, and awoke one morning dizzy, *nauseated and vomiting.* He became unusually drowsy. His bowels remained regular without the use of cathartics. He called the doctor because he thought he had "indigestion." He had a slow pulse, no fever except on one occasion and then it was slight, a slightly increased white cell count, sluggish reflexes and very poor ocular convergence. His course paralleled that of the preceding one.

*Case* 3.—A nursemaid, single, thirty-five years old, had a mild attack of "flu." A week later, she felt *nauseated and vomited.* Her menses were regular. She had no fever. She had no bowel disturbances. She had a slight headache. She had no eye symptoms or findings. She was sleepy and tired. The vomiting stopped after three days, and except for malaise and somnolence, she has been all right since.

*Case* 4.—A lunch-room owner awoke one morning with *nausea, vomiting* and diarrhoea. He had a slight fever and leucocytosis. His wife who had eaten the same kind of food as he at both the noon and evening meals of the preceding day was well. After a week, the vomiting and diarrhoea gradually disappeared, but he remained drowsy and tired for sometime thereafter.

*Case* 5.—A married woman 35 years old with negative Wassermann and Kahn tests had had several induced miscarriages. Menses were painless and regular and vaginal examination revealed no tenderness nor masses. She denied having had the "flu" but the other members of her household had it "bad." She began to have trouble

keeping type in focus when reading, and a month later went to see the doctor because of *nausea, vomiting* and malaise. She had a slight fever and slight leucocytosis. She also improved gradually.

As may be noted in the above cases, superficially there is much resemblance to a host of ordinary conditions such as tabes, pregnancy, food poisoning, or salpingitis. The following symptoms seem to be more or less characteristic of this disease, although they are seldom all found in the same patient:

Vomiting without necessarily abdominal pain or diarrhoea;
nausea, continuous or remittent;
vertigo;
somnolence, often followed by insomnia;
marked malaise;
eye disturbances or symptoms referable to the labyrinth;
fever, very slight and intermittent;
leukocyte count slightly elevated;
course of several weeks to several months.

Spinal punctures were not done because even in advanced cases of lethergic encephalitis there are seldom marked changes in the fluid pressure, globulin or cell count.

Of course there is no absolute proof of the specificity of such cases, even though they go on into the advanced stages of paralysis agitans! For that matter, the causative organism of "influenza" has never been positively identified, nor its relation to the epidemic encephalitis of 1918 indisputably established.

There are individuals who suffered with extreme malaise, vertigo, somnolence and vomiting after they had a mild attack of "flu" in 1918, and who state that they have never felt that they completely recovered. Some of them still have slight visual disturbances and other chronic ailments on a nervous basis.

Attention is directed to these cases in the hope that more specific diagnoses can be made and that the situation will become clarified through wide-spread recognition and study.

## Conclusions

Unusual cases of vomiting have appeared during the recent epidemic of "influenza."

These seem to bear a close relation to lethargic encephalitis.

Vestigial disturbances remain in many individuals similarly affected during the pandemic of 1918.

# Summary of Investigations on the Etiology of Tropical Sprue in Porto Rico*†

By Charles Weiss, Ph.D., M.D., Francisco Landron, B.Sc., Oscar Costa-Mandry, M.D., D.M., and Dorothy Wilkes-Weiss, M.D.

THERE has been noted in recent years a growing interest in the study of so-called "tropical sprue". This is due largely to the increasing number of cases recognized in sub-tropical and temperate regions. For example, Thaysen reports five cases of sprue originating in Denmark; Lambright describes a case from Cleveland, and the observations of Wood in North Carolina and Silverman in Louisiana show that the disease is not at all uncommon in those states.

A second stimulus has been the suggestion promulgated by Wood, Christian and others, and supported by recent studies on liver therapy in certain types of anemia, that sprue and pernicious anemia are not only closely related disorders but may be phases or stages of the same disease.

It has therefore seemed to the writers that the following summary of studies on sprue in Porto Rico, where as Ashford has frequently pointed out, the disease is prevalent, might be of general interest.

*I.—Epidemiology*:

According to the records of the Bureau of Vital Statistics of the Department of Health of Porto Rico there were 322 deaths from sprue during the period July 1, 1924 to December 31, 1927. A large majority of these deaths were distributed among the populous municipal districts, or counties, along the coast, that of Ponce (population 76,200) heading the list with 85 deaths, San Juan, the capital, (91,600), second, with 36 deaths, and Mayagüez (43,000), third, with 27 deaths.

The relatively small number of sprue deaths reported from the high hilly interior, where there is a dense rural population and some ten towns of three to fifteen thousand population at altitudes of 400-2200 feet, may be due to climatic factors, such as lower mean temperature with greater diurnal variations, heavier rainfall, less sunshine, etc., but can be explained by conditions of medical practice. A much larger percentage of the sick in the interior are not attended by physicians, so that diseases like sprue, in which the diagnosis depends on careful examination, are likely to pass unrec-

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†Presented before the American Society of Tropical Medicine at Washington, D. C., May 1, 1928.

ognized. Even in the larger coastal cities where doctors are in reach of everyone, it is well known that certain physicians see many cases of sprue while others report few, the difference being due not so much to variations in clientele as to lack of agreement as respects criteria of diagnosis. (Table I)

| | |
|---|---|
| Under 5 years | 5 cases |
| 5- 9 years | 3 cases |
| 10-19 years | 1 case |
| 20-29 years | 11 cases |
| 30-39 years | 16 cases |
| 40-49 years | 20 cases |
| 50-59 years | 23 cases |
| 60 and over | 6 cases |

It is noteworthy that most of the cases fall between thirty and sixty years. Of these 85 cases, there were 73 Porto Ricans, 10 Continental Americans, 1 Canadian and 1 Arab. While the proportions of Continental Americans to Porto Ricans in the Island is approximately 1:50, the former live largely in San Juan, are mostly well-to-do, and a large proportion seek medical care in the single American Hospital. The figures, therefore, do not support the prevalent idea that sprue is much more common among new-comers than among native residents. The mortality figures of the Health Department, likewise show no

TABLE I

DISTRIBUTION OF DEATHS FROM SPRUE IN THREE GROUPS OF MUNICIPALITIES OF PORTO RICO

| Group No. | Groups of Selected Municipalities | Total Population | Total No. of deaths 2½ yrs. |
|---|---|---|---|
| 1 | Northern Coastal Municipalities* | 239,500 | 82 |
| 2 | Central Mountainous Municipalities | 1,420,000 | 322 |
| 3 | Southern Coastal Municipalities | 231,200 | 155 |
| | Entire Island of PORTO RICO | 231,850 | 32 |

*Group 1 includes Aguadilla, Hatillo, Arecibo, San Juan, Rio Piedras, Rio Grande and Fajardo.

Group 2 includes Coamo, Ciales, Aguas Buenas, San Sebastian, Morovis, Cayey, Aibonito, Caguas, San Lorenzo, Juncos and Humacao.

Group 3 includes Mayagüez, Cabo Rojo, Ponce, Guanica, Salinas, Guayanilla, Yabucoa, Guayama, and Santa Isabel.

In respect to racial incidence, we note that among the recorded deaths from sprue, there were 261 white, and 61 colored, or a ratio of more than 4:1, while the proportion of whites to colored in the general population is officially stated to be about 3 to 1.

There is a slight excess of females over males in the series, the figures being 170 and 152 respectively.

From the records of the Presbyterian Hospital of San Juan (70 beds), where 85 sprue cases were treated from July 1, 1924 to December 31, 1927, the following figures for ages were obtained:

significant differences in the incidence among white and colored.

*II. Etiology*:

In any discussion of the question of etiology several questions always arise.

(a) Is sprue a sequel to wasting diseases of the tropics? A study of the clinical histories of the 85 Presbyterian Hospital cases with special reference to previous or coexisting infections does not support the idea that sprue is a sequel to infection with bacillary or amebic dysentery, malaria, syphilis, tuberculosis, or to the various helminthic infestations, particularly hookworm. While all of these infections except the dysenteries, are fairly common in Porto Rico, no correlation with sprue is evident when the data are tabulated, the associations with any of these infections being no more frequent than among non-sprue cases. (Table II)

Answers of sprue patients to questions as to habits of eating, however, tend to confirm Ashford's theory that excessive indulgence in sweets, breadstuffs, rice, potatoes, and greasy foods, such as lard and olive oil, is a contributory factor in the development of sprue. (An interesting discussion of the food problem in Porto Rico is contained in a recent article by Cook.) It is significant that 60 of the 85 cases, or 70.5 per cent, were discharged as markedly improved, after treatment with a "sprue diet" consisting of selected types of fats, restricted carbohydrates, and an abundance of proteins and vitamins. It has been found that a majority of sprue patients recover normal health on dietary treatment only, without the use of any medication, and that they remain well, if they adhere to the diet. Advanced cases showing the so-called "sprue cachexia," however, may not respond.

(b) Is sprue a transmissible disease?

An attempt was made to transmit sprue to 3 human subjects, all white

TABLE II

SHOWING IMPORTANT COMPLICATING DISEASES AND SIGNIFICANT POINTS IN PAST MEDICAL HISTORY OF 85 CASES OF SPRUE TREATED AT THE PRESBYTERIAN HOSPITAL, SAN JUAN, PORTO RICO,—(1925-1928).

| *Important Complicating Diseases* | | *Significant Diseases in Past Medical History* | |
|---|---|---|---|
| Hookworm | 7 | Typhoid fever | 14 |
| Trichuris trichiura | 8 | Malaria | 19 |
| Ascaris lumbricoides | 3 | Syphilis | 8 |
| Cirrhosis of Liver | 1 | Influenza | 11 |
| Tuberculosis (lung and pleura) | 6 | Tuberculosis | 2 |
| Suspected T. B. | 1 | Dysentery | 2 |
| Cancer of tongue | 1 | Jaundice | 3 |
| Cancer of stomach | 1 | Rheumatism | 7 |
| Ulcer of stomach or duodenum | 2 | | |
| Pyloric Obstruction | 2 | | |
| Syphilis | 1 | | |
| Malarial Cachexia | 1 | | |

Porto Rican adults, by rubbing into their tongues the scrapings from the tongue of a cachectic sprue patient who was suffering with very severe diarrhea, marked psilosis of the tongue with aphthous ulcers and atrophy of the papillae, severe anemia, and atrophy of the liver. These attempts, as well as similar experiments on 3 ring-tailed monkeys (Macacus rhesus), have been thus far unsuccessful. Three monkeys were also fed with feces from this sprue case. Thirteen human subjects were inoculated intra-cutaneously with various living monilia cultures and monilia psilosis cultures were rubbed into the tongues of three monkeys and three persons. In all cases no symptoms of sprue developed up to six months after inoculation.

*III. The rôle of Monilia psilosis (ashfordi) in sprue*:

A majority of our sprue cases have shown M. psilosis in the feces, but confirming the work of Hines, Fairly and Mackie, and others we have found this organism also in many patients who were not suffering from sprue, and have failed to find the fungus in many typical sprue cases. Blood cultures made in eight cases of sprue also showed no monilia. Contrary to the suggestion of several investigators that monilia proliferate in the intestine because of the increased acidity of its contents, and that the fungi disappear when the intestinal contents become alkaline after feeding a special sprue diet, we have observed that *M. psilosis* grows well in infusion broth at pH 6 to 8, the optimum being at 7. Furthermore, when *M. psilosis* is planted in tubes of broth of varying pH (5 to 8), the hydrogen-ion concentration of all tubes after a few weeks tends to reach a pH of about 8, this being the optimum for the survival of this organism.

(a) *Toxic substances in Monilia psilosis.*

It has been asserted that cultures of *M. psilosis* are more toxic for animals than other forms of monilia. Our experiments have shown that, while *M. psilosis* is more toxic than *M. albicans*, we also find that a monilia-like organism, a cryptococcus from cutaneous blastomycosis, is much more toxic than *M. psilosis*. We have been able to demonstrate an endotoxin in cultures of *M. psilosis* which is attenuated by heating at 60°C for one half hour and retained by a Mandler filter. This endotoxin, as well as many other autolysates, extracts and cultures of this organism shows no hemolytic activity against human erythrocytes in vitro. When grown in human blood broth for several days and filtered through a Mandler candle, *M. psilosis*, *M. albicans* and the cryptococcus show evidence of an extra-cellular toxin. This can be demonstrated only by intracutaneous injections into human subjects. These endo- and exotoxins do not, however, manifest any antigenic specificity when tested by the intracutaneous method in a number of sprue patients as well as miscellaneous controls, or in rabbits which had been previously injected with various types of living and killed monilia.

(b) *Skin reactions in sprue with toxins of various monilia.*

The exotoxins of the three monilia

cultures together with the corresponding vaccines of Michel (killed, autolyzed suspensions) were tested on a series of 22 undoubted cases of sprue and on 26 patients suffering from various medical and surgical disorders. The results, indicate that while a large percentage (73) of sprue cases gave positive skin reactions to the exotoxins of *M.psilosis*, a still larger percentage (82) of the same series also reacted to the toxins of *M. albicans* and of a cryptococcus of cutaneous blastomycosis. In the control series (non-sprue patients) about 35 per cent reacted to all three types of toxins. The results with the use of killed autolyzed monilia suspensions (Michel vaccines), as antigens, gave similar comparative results, with lower absolute figures. The sprue cases were 55-64 per cent positive, while the control series were 23-27 per cent positive.

(c) *Monilicidal activity of the whole blood in sprue.*

With the use of the new technic of Bull and Tao, specimens of whole blood taken from a series of 20 sprue patients were compared with blood obtained from 20 miscellaneous hospital patients in their ability to inhibit the growth of various monilia. We failed to demonstrate any specific monilicidal property in the blood of sprue patients, the power to inhibit the growth of monilia being equally possessed by many blood specimens from non-sprue patients.

These immunological investigations, which will be reported in full in later communications, do not support the hypothesis that tropical sprue in Porto Rico is caused by a fungus of the species Monilia psilosis.

*IV. Are the digestive disturbances observed in sprue patients due to a state of hypersensitiveness to specific food stuffs?*

Since our investigations could not substantiate the infectious nature of sprue, it was considered advisable to test the hypothesis that the untoward symptoms of the disease—diarrhea, sore tongue, tympanites, etc., are due to a state of specific hypersensitiveness to certain food stuffs. The foods which most frequently exaggerate the symptoms of active cases or cause relapses in recovered cases, are rice, wheat-bread, potatoes and fats. We therefore, included these in our list of 32 "allergens" to be tested by the "scratch" or "cutaneous" method on a series of 29 sprue patients and 26 miscellaneous controls. The commercially prepared proteins from the food stuffs most consumed in Porto Rico (beans, pork, rice, bread, cod-fish, potatoes, etc.) were used, as were also some of the purified starches obtained from rice, potatoes, and beans, and certain fats (lard, butter, and cocoanut oil) as well as a Porto Rican spice (achiote), a native pepper and coffee. No hypersensitiveness to any of these foods was demonstratable.

*V. Biochemical observations on sprue patients.*

In the course of routine clinical examinations in the laboratories of the Presbyterian Hospital, (San Juan) it was observed that of 30 sprue cases, only five, or 16.7 per cent, had a total

achlorhydria; ten, or 33 per cent, had hypochlorhydria, while the remaining 50 per cent showed a normal HCl content. In contrast to this, it will be remembered that most investigators report 90-99 per cent achlorhydria in pernicious anemia.

The examination of the blood (Folin's methods) for cholesterol, urea, uric acid, creatinin, chlorides and glucose, revealed no significant findings excepting very low cholesterol figures (111.0 and 67.6 mg. per 100 cc. of blood) in a case which was markedly cachectic. The sugar tolerance curves and the phenolsuphonephthalein tests of kidney function did not yield any constant results. (Table III)

## Conclusions

1. With 322 deaths registered from sprue in two years and a half and 85 cases treated in a single 70-bed hospital in the same period, the disease must be considered fairly common in Porto Rico. Natives and continental Americans appear equally susceptible, and no marked difference is noted in the incidence among males and females, and among whites and colored.

2. Inoculation of human volunteers with sprue tongue scrapings and with cultures of *Monilia psilosis* has given negative results. Attempts to transmit the disease to monkeys by similar inoculations and by feeding the feces of sprue patients have been likewise negative.

3. While *Monilia psilosis,* suspected of an etiologic role in sprue, contains an exotoxin as well as an endotoxin, these products do not show any hemolytic activity in vitro. Skin tests on sprue patients and controls with exotoxins and endotoxins of *M.psilosis* also fail to show an immunological relationship. Tests with toxins of two related organisms (M. albicans and a cryptococcus), not suspected of being related etiologically to sprue, have given similar results. It is also found that the blood of sprue patients exhibits no specific monilicidal activity.

4. Sprue patients give no specific cutaneous reaction (scratch test) to any of 32 local foods, indicating that their intolerance to certain foods is probably not to be explained on an allergic basis.

5. Of the common biochemical methods used in clinical examinations, gastric analysis is of the greatest value in the diagnosis of sprue. The rarity of achlorhydria in sprue is an important point in differentiating the disease from pernicious anemia.

## Acknowledgements

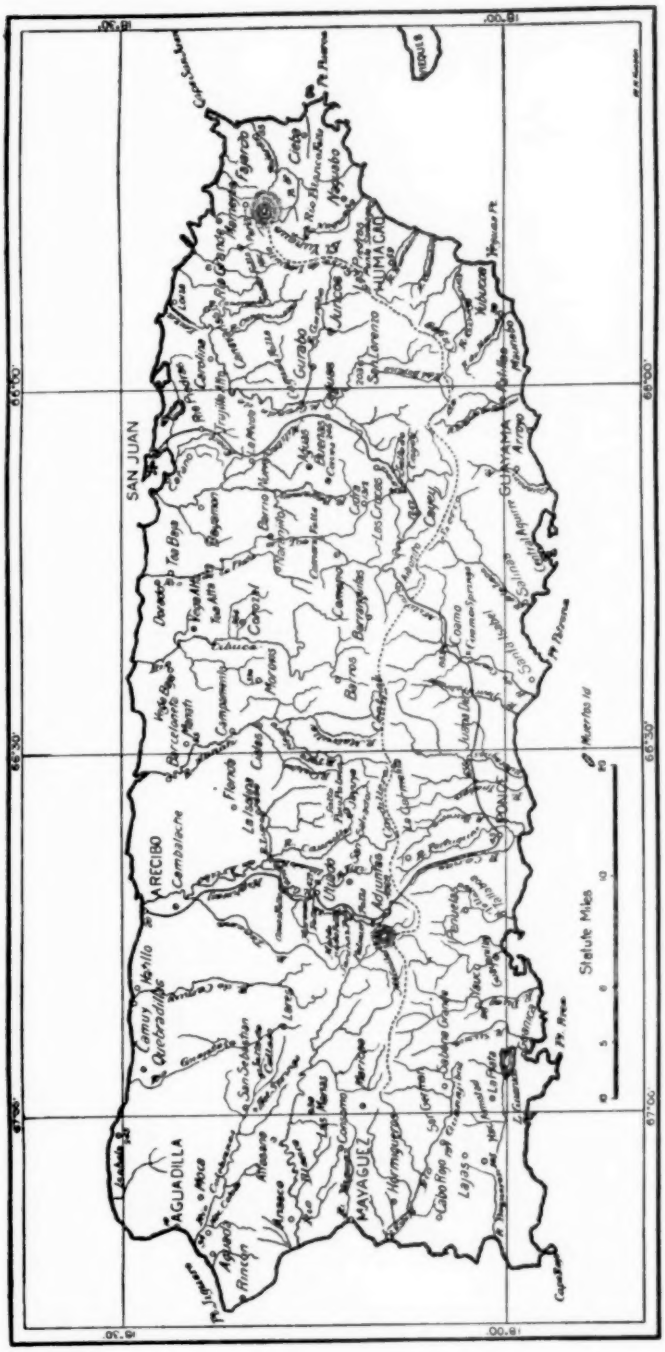
We are indebted to a number of physicians of Porto Rico, particularly Dr. Wm. R. Galbreath, Dr. Walter Glines, Dr. Gary Burke and Dr. Américo Serra of the Presbyterian Hospital, San Juan, for cooperation in carrying out tests on patients under their care. We are especially grateful to Dr. B. K. Ashford for cultures of the several fungi used in the investigations and to Dr. Robert A. Lambert, former Director of the School of Tropical Medicine for very helpful criticism and advice.

TABLE III
BIOCHEMICAL OBSERVATIONS ON SPRUE PATIENTS

| No. Age, Sex, Color, Name. | Clinical History | Clinical Exam. | Blood | Blood Chemistry | | | | Other Laboratory Tests | Special Exam. |
|---|---|---|---|---|---|---|---|---|---|
| 18675<br>10-10-27<br>43 F.<br>W.<br>P.R.<br>Fugencia<br>Enrique. | Weakness, malaise, diarrhea, glossitis. | Emaciated, cachetic. Tongue red glazed and moist small liver, abdomen distended. | R.B.C.—<br>2,410,000<br>W.B.C.—<br>3,550<br>Hbg. 70%<br>Polys 58%<br>Lymph 39%<br>Eos 3% | U.N. 16.8<br>U.A. 2.8<br>Cr. 1.8 | Chol. 460<br>Gl. 82.5 | | | Icteric Index 4.7; Kahn 233<br>Gastric Analysis. (Acidity)<br>Free Total HCL<br>20.0 30.0<br>33.0 50.0<br>45.0 65.0<br>33.0 50.0<br>10.0 30.0<br>20.0 35.0 | Glucose Tolerance Test, mg. per 100 cc.<br>Fasting 82.5<br>1st. hr. 140.0<br>2nd. hr. 110.0<br>3rd. hr. 51.0<br>4th. hr. 107.0<br>Monilia absent in feces. |
| 18699<br>11-11-27<br>32 F.<br>W.<br>P.R.<br>Carmen<br>Robles. | Duration 4 months, weakness and burning of tongue, loss of weight; diarrhea, Beef and fatty foods disagree. | Pale, emaciated. Tongue pale, clean raw edges around tip. Tenderness of abdomen. | R.B.C.—<br>1,300,000<br>W.B.C.—<br>5,800<br>Hbg. 47%<br>C.I.—1.6<br>Polys 60%<br>Lymph 30%<br>Eos. 8%<br>Trans. 2%<br>4 nucleated R.B.C. | U.N. 21.84<br>U.A. —<br>Cr. 1.48 | Chl. 480<br>Gl. 122.4 | | | Gastric Analysis.<br>Free Total<br>15 112.5<br>30 77.5<br>22.5 85.0<br>40 10.0<br>35 85.0 | Monilia absent in tongue and feces.<br>Icteric Index 6.2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 17354<br>10-11-26<br>49 M.<br>W.<br>P.R.<br>Julian Apolinario. | Duration 2½ months, sudden onset, epigastric distress, sore tongue, weakness, 12 stools a day, yellowish foamy; mucus; flatulence. | Tongue raw, clean and smooth, papillae absent on tip and anterior; small liver, dehydrated. Saccharose aggravated. 2 children and father have sprue. | R.B.C.—<br>2,420,000<br>W.B.C.—<br>5,600<br>Hbg. 65%<br>Polys 38%<br>Lymph 57%<br>Poikilo and aniso. | U.N.<br>U.A.<br>Cr. | 16.8<br>—<br>1.23 | Chol.<br>Gl.<br>N.P.N. | 111.0<br>91.74<br>30.15 | Feces trichuris trichiura<br>Rosenthal liver function test normal. | |
| 16924<br>6-14-26<br>44 F.<br>W.<br>P.R.<br>Ana Maria Ruell. | Duration 8 years, diarrhea, dyspepsia, weakness, palpitation and dyspnea; anemia. | Weakness, uncinariasis. | R.B.C.—<br>680,000 to<br>1,720,000<br>W.B.C.—<br>1,200-2,800<br>Hbg. 45%<br>Poikilo and anisocytosis. | U.N.<br>U.A.<br>Cr. | 58.1<br>—<br>— | Chl.<br>Gl.<br>N.P.N. | —<br>—<br>— | Hookworm, ascaris.<br>Gastric Analysis.<br>Free Total<br>40 14<br>35 55<br>30 56<br>0 21.4<br>0 21.6<br>0 30.2<br>Occult bld— | Feces show ascaris.<br>P.S.P.<br>1—45%<br>2—15% |
| 17719<br>1-27-27<br>59 M.<br>W.<br>Am. (Mr. O.) | Loss of weight, weakness, diarrhea, sore mouth, stools 4-8, large, light, frothy, following high carbohydrate diet. Treated for gout. | Emaciated. | R.B.C.—<br>3,920,000<br>W.B.C.—<br>7,300<br>Hbg. 70%<br>Polys 30%<br>Lymph 65%<br>Eos. 2%<br>Trans. 3% | U.N.<br>U.A.<br>Cr. | 18.2<br>—<br>— | Chl.<br>Gl.<br>N.P.N. | —<br>79.5<br>— | Gastric Analysis.<br>Free Total<br>24 52<br>24 52<br>24 54<br>45 75<br>44 72 | P.S.P.<br>1—20%<br>2—20% |

| No. Age, Sex, Color, Name. | Clinical History | Clinical Exam. | Blood | Blood Chemistry | | | | Other Laboratory Tests | | Special Exam. |
|---|---|---|---|---|---|---|---|---|---|---|
| 18721<br>11-15-27<br>33 M.<br>W.<br>P.R.<br>Taboa. | Diarrhea 4 months, loss of weight (25 lbs.), weakness; stools 6 a day, pain and burning in tongue. | Very thin. Tongue red and beefy. | R.B.C.— 3,600,000<br>Hbg. 86% | U.N.<br><br>U.A.<br>Cr. | 8.4<br><br>2.4<br>1.3 | Chl. 465<br>Gl. —<br>N.P.N. — | | Gastric Analysis.<br>Free / Total<br>0 / 7.5<br>5.0 / 17.5<br>17.5 / 32.5<br>17.5 / 40.0<br>17.5 / 37.5<br>20.0 / 40. | | Monilia absent in feces and tongue.<br>Icteric Index 4.4. |
| 50 F.<br>W.<br>P.R.<br>A. Santiago. | Duration 3 years. Tenesmus, white diarrhea with mucus; loss of weight, severe flatulence, sore tongue. | Emaciated; sore tongue; diarrhea. (Carcinoma of pancreas?) | Secondary aenemia.<br>R.B.C.— 3,300,000<br>W.B.C.— 7,500<br>Hbg. 60%<br>Polys 65%<br>Poikilo, etc. | U.N.<br><br>U.A. | 14.0<br><br>— | Chl. —<br>Gl. 155<br>N.P.N. 35.7 | | P.S.P.<br>1st. 35%<br>2nd. 30%<br>Gastric Analysis shows no free acid. | | Monilia present on tongue.<br>Icteric Index 4.57. |


SAN JUAN
ARECIBO
AGUADILLA
MAYAGUEZ
HUMACAO
GUAYAMA
PONCE
Statute Miles

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# Diabetes Mellitus: A Further Study of the Etiology of the Disease*

By John C. Krantz, Jr., *Baltimore, Md.*

## Introduction

RECENT literature indicates the existence of a hyperglycemic principle in the blood of diabetic animals. Thus L. Kepinov and S. Petit-Dutailis (1) showed the existence of a principle in diabetic blood which acts antagonistically to the action of insulin. These investigators depancreatized dogs to the extent that a normal blood sugar was just maintained: in these dogs the injection of large quantities of diabetic blood produced a hyperglycemia which lasted for several days. Depisch and Hasenohrl (2) found the serum from a case of diabetes with a paranephritic abscess to have an insulin-inhibiting action on rabbits. Serum from cases with diabetes but without sepsis did not show this effect, and cases with sepsis but without diabetes did not show it.

Of special importance is the work of Bergey (3) who has conducted a series of experiments in which he produced glycosuria in rabbits by the intravenous injection of diabetic urine which had been passed through a Berkefeld filter. Serum broth which was inoculated with diabetic urine and cultivated under aerobic conditions for fifty-six days, was found by this investigator to produce glycosuria when injected into rabbits. Very recently certain other investigators (4 and 5) in this field have failed to observe the infectivity of diabetic urine as noted by Bergey. The present author considered this work of epoch-making importance in the etiology of diabetes mellitus and began a series of investigations, to further substantiate, if possible, the existence of the virus of diabetes, by the phyto-pharmacological method of Macht (6, 7 and 8) and his collaborators.

## Experimental

### 1. *Effect of Intravenous Injections of Diabetic Urine.*

Ten rabbits weighing from 1.5 to 2 kilos were fasted for 24 hours, and blood sugar determinations (9) made, and the filtrate obtained, by passing the diabetic urine through a Berkefeld filter, was immediately injected intravenously. Each rabbit received 2 c.c. of diabetic urine and the controls received 2 c.c. of normal urine. The urines were obtained from the metabolic laboratory of the Johns Hopkins Hospital. The patients were suffering

*From the Laboratory of Pharmaceutical Research, Sharp and Dohme, Baltimore, Md.

with moderately severe cases of diabetes mellitus; some under dietary control alone and others were using insulin. Three of the four diabetic urines gave a strongly positive reaction with Benedict's solution, whereas the fourth one produced only a very faint green turbidity with the same reagent. The urines gave negative reactions for acetone and diacetic acid. Table I records the results of these injections.

TABLE I

Effect of Intravenous Injections of Urine upon the Blood Sugar of Rabbits.

| Rabbit No. | Urine of Patient 2 c.c. | Fasting blood sugar mgm. per 100 c.c. | Blood sugar 8 days after injection. mgm. per 100 c.c. | Blood sugar 16 days after injection. mgm. per 100 c.c. | Glycosuria of Rabbit | Days survived after injection |
|---|---|---|---|---|---|---|
| 1 | E.L. diabetic | 82 | | | — | 6 |
| 2 | E.L. | 87 | | | — | 7 |
| 3 | M.T. diabetic | 76 | 79 | | — | 12 |
| 4 | M.T. | 74 | | | — | 7 |
| 5 | J.S. diabetic | 74 | | | — | 6 |
| 6 | J.S. | 87 | 95 | 45 the day before death | — | 17 |
| 7 | G.W. diabetic | 82 | | | — | 1 |
| 8 | G.W. | 87 | | | — | 7 |
| 9 | J.C. normal | 98 | 89 | | — | |
| 10 | J.C. normal | 106 | 79 | | — | 15 |

The results recorded in Table I indicate that the intravenous injections of diabetic, as well as normal urine, are very toxic to rabbits and in those cases in which the rabbits survived there was no evidence of hyperglycemia. Through the kindness of Dr. James C. Munch of these laboratories an autopsy was made on rabbit No. 5, which revealed degeneration and cirrhosis of the liver and kidney congestion especially of the cortico-medullary boundary. Having determined the toxic nature of the intravenous injections of urine, the next phase of this

investigation had for its purpose the study of the influence of subcutaneous injections of diabetic and normal urine.

*2. Influence of Subcutaneous Injections of Diabetic Urine.*

The fasting blood sugars of five rabbits were determined. Two were injected with a diabetic urine, which had been passed through a Berkefeld filter. Two others were injected with the urine of another patient and the fifth was injected with urine from a normal person. As in the previous experiments these rabbits weighed between 1.5 and 2 kilos and each received 2 cc. of urine; in each case injected subcutaneously.

These diabetic urines were obtained from the University of Maryland Hospital; each patient was suffering with moderately severe diabetes. Each urine gave a strong positive reaction to Benedict's Solution, but was acetone and diacetic acid free. Table II records the results of these injections.

The results obtained by the subcutaneous injections of urine indicate that, although the percentage of rabbits surviving is greatly increased, there is no evidence of these injections producing the cardinal symptoms of diabetes mellitus. It is true that the fasting blood sugar of rabbit No. 14 was somewhat high eight days after injection, but its return to normal seems to indicate that this was a transient hyperglycemia possibly due to fright rather than the typical permanent hyperglycemia of diabetes mellitus.

TABLE II.

Effect of Subcutaneous Injections of Urine upon the Blood Sugar of Rabbits.

| Rabbit No. | Urine of Patient 2 c.c. | Fasting blood sugar mgm. per 100 c.c. | Blood sugar 8 days after injection. mgm. per 100 c.c. | Blood sugar 16 days after injection. mgm. per 100 c.c. | Blood sugar 24 days after injection. mgm. per 100 c.c. | Glycosuria of Rabbit |
|---|---|---|---|---|---|---|
| 14 | M.K. diabetic | 128 | 192 | 97 | 111 | — |
| 94 | M.K. diabetic | 97 | 113 | 106 | 109 | — |
| 95 | M.C. diabetic | 120 | 120 | 74 | 104 | — |
| 64 | M.C. diabetic | 109 | 125 | 64 | 114 | — |
| 84 | J.C. normal | 116 | 82 | died at this time | | — |

3. *Effect of Subcutaneous Injections of Serum Broth Inoculated with Diabetic Urine.*

Fifty tubes of serum broth were inoculated with varying quantities of the Berkefeld filtrate obtained from the urine of three diabetic patients. (University of Maryland Hospital). These tubes were cultivated for 56 days and their effect upon the fasting blood

TABLE III.
Effect of Subcutaneous Injections of Serum Broth Inoculated with Diabetic Urine. Cultivated 56 days.

| Rabbit No. | 1cc. serum broth | Fasting blood sugar mgm. per 100 c.c. | Fasting blood sugar 8 days after injection mgm. per 100 c.c. | Fasting blood sugar 16 days after injection mgm. per 100 c.c. | Glycosuria of Rabbit |
|---|---|---|---|---|---|
| 2 | M.C. diabetic | 104 | 159 | 129 | — |
| 16 | J.C. normal | 84 | 137 | 119 | — |
| 56 | M.DeV. diabetic | 115 | 129 | 127 | — |
| 62 | M.P. diabetic | 116 | 119 | 119 | — |

TABLE IV.
Effect of Subcutaneous Injections of Serum Broth Inoculated with Diabetic Urine. Cultivated 76 days.

| Rabbit No. | Serum broth 1cc. | Fasting blood sugar mgm. per 100 c.c. | Fasting blood sugar 8 days after injection mgm. per 100 c.c. | Fasting blood sugar 16 days after injection mgm. per 100 c.c. | Glycosuria of Rabbit |
|---|---|---|---|---|---|
| 41 | J.C. normal | 114 | 116 | 105 | — |
| 43 | M.C. diabetic | 122 | 135 | 104 | — |
| 48 | M.DeV. diabetic | 111 | 116 | 119 | — |
| 91 | M.P. diabetic | 111 | 111 | 114 | — |

sugar of rabbits studied. A control of normal urine was prepared also. Table III records the results of these injections.

The results of the subcutaneous injections of serum broth recorded in Tables III and IV indicate that there was no hyperglycemia or glycosuria produced.

4. *Phytopharmacological Experiments.*

In order to determine the toxicity of the serum broth inoculated with normal and diabetic urine after 46 days, the cultivation upon the seedlings of Lupinus albus the method employed by Macht and his associates, particularly Macht and Rowe (10), was used. These cultures of serum broth were extremely toxic to plant protoplasm, as indicated by the results given in Table V.

The extreme toxicity of these cultures to plant protoplasm made it impossible to study quantitatively the relative toxicity of the urines in this medium. A study of Table V indicates that these values (Index of growth of the seedlings) have no quantitative significance; however, it is of interest to observe, that the culture made with normal urine is just as toxic as those prepared with diabetic urine. A more significant phytopharmacological observation was made when the blood serum of rabbits injected subcutaneously with normal urine was compared with the serum of rabbits injected subcutaneously with the diabetic urine.

The result of this experiment is recorded in Table VI.

The results recorded in Table VI indicate that the blood serum of rabbits injected subcutaneously with diabetic urine is no more toxic to plant protoplasm than the serum of those injected with normal urine.

TABLE V.
Phytopharmacological Study of Serum Broth Inoculated with Urine.

| No. | | Index of Growth of Seedlings: Percentage |
|---|---|---|
| 1 | In Shive Solution (11) | 100 |
| 2 | Urine of patient, M. DeV. diabetic, in serum broth, 0.83 per cent conc. broth in contact with seedlings. | 13.0 |
| 3 | Same as 2 but 1.7 per cent conc. | 14.0 |
| 4 | Same as 2 but 0.41 per cent conc. | 30.0 |
| 5 | Same as 2 but 2.5 per cent conc. | 12.0 |
| 6 | Urine of patient J. C. normal in serum broth 0.33 per cent conc. broth in contact with seedlings. | 17.5 |
| 7 | Same as 6 but 0.66 per cent conc. | 18 |

TABLE VI.

A Phytopharmacological Study of Blood Serum of Rabbits.*

| No. | | Index of Growth of Seedlings Percentage |
|---|---|---|
| 1 | In Shive Solution | 100 |
| 2 | 1 per cent Blood Serum of Rabbit 84 injected with normal urine | 86 |
| 3 | 1 per cent Blood Serum of Rabbit 94 injected with diabetic urine | 84 |
| 4 | 1 per cent Blood Serum of Rabbit 95 injected with diabetic urine | 90 |
| 5 | 1 per cent Blood Serum of Rabbit 64 injected with diabetic urine | 74 |
| 6 | 1 per cent Blood Serum of Rabbit 14 injected with diabetic urine | 76 |
| 7 | Same as 6 | 75 |

*These phytopharmacological experiments were conducted 18 days after 2 c.c. subcutaneous injections of urine.

## DISCUSSION OF RESULTS.

The experimental data correlated in this investigation of a zoölogical and phytopharmacological nature seem to contraindicate the existence of a diabetic principle responsible for the transmissibility of the disease, by the methods herein described. It is possible, that as the former mentioned investigator (3) obtained glycosuria by these methods, that the presence of glucose in the urine was caused by a lowered renal threshold due to kidney impairment, as no blood sugar determinations are recorded. In no instance was the present author able to produce glycosuria in rabbits by the injection of diabetic urine and no marked permanent hyperglycemia resulted.

## CONCLUSIONS

From the zoölogical and phytopharmacological experiments herein described, evidence has been produced, which seems to contraindicate the existence of a virus of diabetes which in turn may be responsible for transmissibility of diabetes mellitus.

The author is indebted to Mr. C. Jelleff Carr for his technical assistance during this investigation.

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# Our Debt to Aristotle

By L. J. Moorman, M.D., F.A.C.P.

THREE hundred and eighty-four years before Christ came to Bethlehem Aristotle was a babe in ancient Macedonia. From the womb of Phoestis had sprung the master mind of all ages "The sovereign lord of the understanding." Two and a half centuries before Saint Paul received the call for help in Macedonia, this little kingdom, resting quietly on the fringe of Athenian glory, had sent into the world the first evangel of natural history and the rightful progenitor of all the positive sciences: The author of logical thinking and the stabilizer of metaphysics.

Aristotle was born in the little town of Stagira. He was of Greek lineage. Phoestis, his mother, belonged to Chalcis, where Aristotle took refuge from his enemies during his last days. His father, Nicomanchu, was a doctor, tracing his descent and his art to Machaon, a son of Aesculapius.

The King of Macedonia came to Stagira annually to hunt wild boar and Nicomanchu served as physician for the royal hunting party. Aristotle's mother being dead, he was permitted at a tender age to accompany his father on these difficult and dangerous excursions. It is said that the king became very much attached to Aristotle and was pleased to have him as a companion for his own son Phillip. Although Nicomanchu was killed by an avalanche of sliding stone while Aristotle was still quite young, the king continued to include him in his party for the annual hunt, because of his good spirits, his unbounded energy and endurance. It is said that Aristotle declined an invitation to become a resident in the Royal Palace in order that he might go to Athens to study at the School of Plato. However he was destined to enter ultimately the royal court as Alexander's tutor, rather than as a companion to Phillip, who was to become the father of the World Conqueror.

At the age of eighteen, in the year 366 B. C., Aristotle came to the Greek metropolis and attached himself to the School of Plato where he remained for twenty years. Plato was then 60 years of age. Socrates was about the same age when Plato became his pupil. Socrates spent his energies redeeming the individual man, while Plato sought to redeem the world. Yet Plato was true to his Socratic teaching in that he "sought truth with his soul." He accepted the simple message of Socrates that "behind every living form there is the divine reality of life itself." Aristotle soon attracted the attention of Plato and as time passed their intellectual differences served to control their affection for each other. In one

breath Plato would refer to Aristotle as the genius of his school and in another he would ridicule him for seeking knowledge in books. These mental differences which separated the master and pupil ultimately divided the world into two camps: The Platonists and Aristotelians.

Aristotle was not a materialist; he believed in God, but his methods of study differed from those of Plato. While Plato contemplated the universe in a mystical, soul-satisfying manner, Aristotle gathered knowledge by reading, by talking with people in all walks of life, especially those having intimate contact with living creatures; and, of greater significance, he acquired knowledge by a close analytical study of living forms. He was a true biologist over two thousand years before Lamarck coined the term "Biology". This method of study was considered an unwarranted innovation and was looked upon with contempt by Athenian Philosophers. Aristotle had not only aroused the criticism of Plato by reading books, but he had brought upon his head the contempt of Athenian culture by descending from the peaks of Platonic teachings to "Grub for knowledge in the base earth of natural history." It must have required courage little short of that exhibited by Socrates for this young student, an outlander from the unpopular court of Macedonia, to pursue his studies and demonstrate his methods in the city of Athens: To literally recall the wandering soul from star-gazing and day-dreaming to the facts of man's earthly existence. We may safely say that Aristotle originated the systematic study of natural history. In other works, he founded the sciences of comparative anatomy, systematic zoölogy, embryology, teratology, botany and physiology. He definitely laid the foundation upon which rests all modern scientific research.

While Phillip and Alexander the Great were soon to occupy the center of the world stage because of the invincible march of the Macedonian phalanx, time has proven that the destinies of the human race rested not in the hands of these conquering monarchs, but in the methods of the quiet reader and teacher whose voice was destined to carry through the centuries, penetrating the black night of the Dark Ages to take part in the revival of learning and to guide the progress of science, thereby enriching modern life in innumerable ways, through all the different avenues of scientific study and research. During the twenty years spent in Plato's school Aristotle must have carried his studies in natural sciences far beyond the point where Plato or any other member of the school could have carried him.

When Plato died Aristotle, because of growing prejudices, deemed it wise to leave Athens. He became a member of the Court of Hermias, a former fellow-student, who had become King of Atarneus. He married the niece of his royal friend and possibly anticipated the probability of wearing the crown in case something should happen to the King. Hermias passed by way of the dagger, revolution ensued and Aristotle was relieved of an embarrassing situation when messengers

arrived from King Phillip of Macedonia, Aristotle's former playmate, urging him to undertake the education of Alexander who was then thirteen years of age. This was apparently a most fortunate coincidence for two of the world's greatest characters. It is impossible to say what might have been the result if Phillip had not selected Aristotle as his son's tutor.

Alexander repeatedly gave credit to Aristotle for the various elements of success which were so manifest in his character and Aristotle must have fully realized the importance of the contributions Alexander made to advance the study of natural history. It is easy to trace, through Alexander, Aristotle's influence upon medical history. Aristotle was a student of animal life and he was a great lover of the horse. It seems that he and his pupil Alexander made a special study of the horse and in the course of this study they set up a complete skeleton and Aristotle prepared an essay which served as the last word on the subject for eighteen hundred years, when the genius of Leonardo da Vinci was fired by Aristotle's essay and the serious study of the horse was renewed by dissecting and painstaking drawings. It is reasonable to believe that Leonardo's interest in natural science was largely inspired by Aristotle's influence. Osler refers to him as being "Insatiate in experiments, intellectually as greedy as Aristotle." In discussing the great anatomists and the keen students of the human form, Osler further says: "But greater than any of these and antedating them is Leonardo da Vinci, the one universal genius in whom the new spirit was incarnate, the Moses who alone among his contemporaries saw the promised land."

In the year 335 B. C., soon after the death of Phillip, Aristotle returned to Athens and established his famous school in the grove of Apollo, favorite haunt of Socrates. Here he spent the most fruitful years of his life, teaching and collecting manuscripts, maps and objects to illustrate his lectures, especially those on natural history. It is said that Aristotle had the first zoölogical garden and the first museum of natural history in the world. Alexander is said to have given him eight hundred talents to enable him to form this collection and to have laid all the hunters, fowlers and fishermen of the Macedonian Empire under injunctions to report to Aristotle any matters of scientific interest that they observed.

The first of the world's great libraries was here established and those of Alexandria and Pergamon followed. With the exception of Alexander's contribution toward Aristotle's scientific studies, his one lasting accomplishment is Alexandria and it may be truthfully said that the building of this great city and center of learning was a monument to Aristotle's influence in the life of the world conqueror.

After referring to Vesalius, who was born in 1514, as the real father of anatomy, Doctor W. W. Keen says, "If we wish to see its starting-point, we must go back to ancient times—we must retrace our steps to the third century before Christ and transfer ourselves from the amphitheatre of

Padua to that of Alexandria, to discover the bold innovators who first forced the dead human body to disclose its secrets for the benefit of the living." These innovators were Herophilus and Erasistratus who, indirectly through the influence of Aristotle, dissected not only the dead human body but the living as well, in order to search for the hidden springs of life. For centuries the study of anatomy was centered in Alexandria and in the second century after Christ Galen was compelled to go from Pergamus to Alexandria in order to see a skeleton. The dissection of the human body disappeared from the face of the earth for a period of twelve centuries. In Alexandria, this ancient stronghold of science, where tardy tolerance first permitted the dead body to yield to the hand of the investigator its anatomic secrets, Clot Bey, seventeen centuries after dissection had been discontinued, attempted to demonstrate anatomy by the use of the dead body and while in the act of opening the thorax was stabbed by one of his own students, evidently acting under the urge of an insane prejudice against the mutilation of the human form.

We might cite many examples of Aristotle's influence as manifested either directly or indirectly, but we must hasten to consider briefly the specific relation of his life and work to the development of medicine. According to Voltaire his recorded studies on animal life formed the best book of antiquity. While Aristotle stood among the first in intellectual attainments, swaying as he did the domains of logic, psychology, ethics, metaphysics, rhetoric, poetry and politics, he was far ahead of his time in the study of natural history. In Darwin's "Life and Letters" we find this statement, "Linnaeus and Cuvier have been my two Gods, though in very different ways, but they were mere school boys to old Aristotle." Aristotle mentions five hundred different animals. Some of his references are worthless, but many of them show a minuteness and accuracy of knowledge which could have come only through the most careful and thorough study. We find that he dissected fifty different kinds of animals and there is sufficient evidence to warrant the belief that he dissected the human embryo. He describes in a comprehensive way the development of the embryo chicken and detected on the fourth day the presence of the heart "beating and moving as though endowed with life." He accurately stated many facts in natural history which were overlooked by other observers for centuries. He was not only the first to collect on a large scale the available information concerning the animal species, but he was the first to undertake their classification. His main divisions are the sanguineous and the bloodless animals, corresponding to our vertebrates and invertebrates. While he realized the difficulties of classification, he did his work so well, there was no further advance in this direction until the time of Linnaeus in the eighteenth century.

Aristotle's discussions of anatomy and physiology show breadth of knowledge, which is astounding when considered in the light of the age in

which he lived. His discourse on the determination of sex is a magnificent analysis. After overthrowing the theories of Empedocles, Democritus and Hippocrates, he presents a theory which though absurd in certain of its phases, has the virtue of placing the determination of sex at the very beginning of embryonic development. In this respect Aristotle was 2200 years in advance of modern science. In a discourse of the qualities by which the parts of animals differ we are astonished to find him discussing the fluctuating characters with something of the same understanding which Mendel applied over two thousand years later.

Sedgwick recently undertook to prove that every mother can nurse her baby and his method of milk expression has been heralded to the world as a most useful discovery. Twenty-two hundred years ago Aristotle stated that "cases have been known where women advanced in years, on being submitted to the process of milking, have produced milk and in some cases in sufficient quantities to enable them to suckle an infant."

In discussing nutrition of the animal body, Aristotle, after describing the stomach and intestines, says there must be something to receive the nutriment from these organs and states that "This something is furnished by the blood-vessels which run throughout the mesentery from its lowest part right up to the stomach." Though the world waited nearly two thousand years for Harvey to prove the circulation of the blood, Aristotle was not far from the truth when he writes as follows: "It is but rational that the flow of blood should extend, as it does, throughout the whole body", and again after describing the watercourses in the gardens, he says, "Now just after the same fashion has nature laid down channels for the conveyance of blood throughout the whole body." The following quotations furnish convincing evidence that Aristotle gave serious attention to the blood and its movement in the body: "Blood beats or palpitates in the veins of all animals alike all over their bodies, and blood is the only liquid that penetrates the entire frames of living animals, without exception and at all times, as long as life lasts." If blood is removed, or if it escape in any considerable quantity, animals fall into a faint or swoon; if it be removed, or if it escape in an exceedingly large quantity, they die. If the blood gets exceedingly liquid, animals fall sick; for the blood then turns into something like ichor, or a liquid so thin that it at times has been known to exude through the pores like sweat. In some cases blood, when issuing from the veins, does not coagulate at all, or only here and there. Whilst animals are sleeping the blood is less abundantly supplied near the exterior surfaces, so that, if the sleeping creature be pricked with a pin, the blood does not issue as copiously as it would if the creature were awake." Aristotle considered the heart the center of the sensory, the motor and the nutritive faculties. Perhaps next in importance he considers the brain, in his words, "The head has also been chosen by nature as the part in which to set some of the senses."

Aristotle was evidently a close student of the diseases of the human body and their pathology. This is proven not only by frequent references found in his extant works on natural history, but by the fact that he refers to his own treatise on the Principles of Diseases. However, if such a treatise was written, history has left no record of it. The following serve to illustrate his numerous references to diseases and pathology: he discussed somewhat in detail hemorrhages from the wind pipe; stones in the gall bladder, kidneys and urinary bladder; intestinal worms, hydrophobia and diseases of the heart, revealing a comparative study of the heart in animals dying of disease and animals killed for sacrificial purposes. Discussing the bites of serpents, he refers to the asp and says, "The so-called septic drug is made from the body of the animal, and is the only remedy known for the bite of the original." This might be considered a crude anticipation of the present method of treatment with antivenom. He refers to the human kidney as a lobulated organ and advances this as a reason for the incurability of Bright's disease over two thousand years before the name was supplied. This reference to the kidney as a lobulated organ further substantiates the belief that Aristotle dissected the human embryo. He was fairly familiar with the problems of nutrition and recognized the evils of obesity.

In giving advice to Alexander, Aristotle displays an amazing sense of sanitary science. After cautioning against idleness and overwork he makes this startling statement: "Do not let your men drink out of stagnant pools—Athenians, city born, know no better. And when you carry water on the desert marches, it should be first boiled to prevent its getting sour." This advice antedating typhoid vaccine twenty-three hundred years might have worked well at Chickamauga. It showed clearly that Aristotle recognized that the chief foe of an army may reside in its own camp, or that disease may exact a heavier toll than war itself. The efficacy of his principles is supported by the fact that Alexander's losses were chiefly in men killed on the field of battle.

In "De Parva Naturalia" Aristotle gives the following conception of the scientist and the physician: "But health and disease also claim the attention of the scientist, and not merely of the physician, in so far as an account of their causes are concerned. The extent to which these two differ and investigate diverse provinces must not escape us, since facts show us that their inquiries are, at least to a certain extent, conterminous. For physicians of culture and refinement make some mention of natural science, and claim to derive their principles from it, while the most accomplished investigators into nature generally push their studies so far as to conclude with an account of medical principles." Virchow in "Die Cellular Pathologie" was merely recognizing the efficacy of Aristotle's methods when he said, "We are in the midst of a great reform in medicine. In our day for the first time the full domain of this so comprehensive field of learning has been laid open to scientific research. Doctrines

that belong to the oldest traditions of mankind are put to the test not only of experience, but of investigation. For experience proofs are demanded, for research accurate methods."

Aristotle had an abiding passion for truth. It was this that strained his position with Plato. While his love for Plato was great, his love of truth was greater. In spite of his commanding genius, his theories often fell hopelessly short of the mark and many times he wandered far from the object of his affections. Fortunately, science was not dependent upon the accuracy of his theories, but upon the method of his procedure; its foundation stands securely upon what he did and not upon what he thought. Aristotle was repeatedly guilty of thinking wrongly, but he never committed the crime of thinking indifferently. As a memorial for Aristotle and an inspiration for us, I have chosen the words of Maurice Maeterlinck, "Our dead are greater and more truly alive than we are; when we forget them, it is our whole future that we lose sight of; and when we fail in respect to them, it is our immortal soul that we are trampling under our feet."

# Editorial

## *MORBUS CAERULEUS*

The phenomenon of cyanosis of the skin and mucous membranes, usually spoken of as *Cyanopathia* or *Morbus Caeruleus,* associated with certain cases of congenital heart disease, has long been a problem about which much discussion has been waged and varying views have been offered in explanation of its etiology. The oldest of these views is that of de Senac (1749), who advanced the theory that the cyanosis is due to a mixture of venous and arterial blood. Supported by Gintrac, Corvisart and many other authorities, this view has been refuted by Peacock and others, on the ground that cyanosis is not always present in cases in which there is a free mixture of venous and arterial blood. In some of the cases of the most severe type of congenital cardiac lesions, in which there was complete mixture of arterial and venous blood, such as cor biatriatum triloculare and persistent truncus arteriosus, cyanosis has been absent. Nevertheless Senac's theory is still applied to the explanation of *cyanose tardive,* a terminal cyanosis occurring in septal defects and patent ductus arteriosus, due to alterations in pressure causing a flow of venous blood from right to left through the defect into the arterial stream. This anomalous venous current into the arterial circulation is regarded by Abbott as the chief cause or the essential factor in the great majority of cases of morbus caeruleus. In 1761, Morgagni advanced the theory of venous stasis in explanation of congenital cyanosis. Supported by Louis and Peacock, this view has been widely accepted, although failing to explain the situation completely. The absence of edema and anasarca in the majority of cases of the morbus caeruleus, the late appearance or absence of the cyanosis in pulmonary stenosis, made it seem very probable that some other cause in addition to mechanical venous obstruction must operate to produce the cyanosis. Cases reported in the literature of pulmonary stenosis with closed septa, with no opportunity for a venous-arterial shunt, that showed no cyanosis at all, or only a slight degree, even in adult life, provide further evidence against venous stasis as a factor in the production of congenital cyanosis. With the theories of mixture of arterial and venous blood and venous stasis regarded as inadequate to explain the etiology of morbus caeruleus, modern writers upon the subject have accepted the theory of deficient aëration of the blood as the essential factor in the production of cyanosis, whether produced by the direct flow of venous blood into the arterial stream or by obstruction to the flow of venous blood to the lungs. Abbott regards the matter as fully settled, that congenital cyanosis depends upon deficient oxygenation; that the

circulation can evidently accommodate itself to a certain degree of oxygen unsaturation, whether brought about by venous stasis, mixture of venous and arterial blood, or by a general slowing up of the whole circulation, but that as soon as this oxygen unsaturation reaches a certain limit, this becomes insufficient for the needs of the body and cyanosis results. Certain secondary factors, such as dilated peripheral capillaries, dark color of the skin, and polycythemia may serve to increase the degree of discoloration, but these factors she regards as concomitant and not primary etiologic factors. In complicated cardiac defects probably all of these factors combine to produce the characteristic mulberry hue and the respiratory symptoms of typical morbus caeruleus. She bases this conclusion upon the monograph of Lundsgaard and Van Slyke on cyanosis. With the principle, that cyanosis is produced by an increase of the reduced hemoglobin in the capillary circulation above a definite threshold value (6.7 per cent), as the basis for the explanation of its occurrence, these authors classify the possible causes of such an increase into: *Modifying factors* which may alter the threshold value of oxygen unsaturation at which the visible manifestations of cyanosis may appear, but which in themselves cannot produce such an increase, as thickness or pigmentation of the skin, altered color of the plasma, raised hemoglobin content of the blood, and variations in the number, size and extent of the capillaries of the skin; and *influencing factors,* which directly produce cyanosis by raising the oxygen-unsaturation of the capillary blood above its threshold value. These determining factors may act in two ways, either by lessening oxygenation in the lungs or by increasing oxygen consumption in the tissues, and there are four of these causative factors: Lessened oxygenation in the pulmonary alveoli, a right to left shunt of venous blood into the arterial stream, an increased reduction of oxygen in the tissue capillaries and the total hemoglobin content. This fourth factor cannot produce oxygen unsaturation in itself, but is of importance in raising this to the threshold value in the presence of any of the other causes. Thus, when the hemoglobin content is very low as in severe anemia, cyanosis will not appear until the oxygen-unsaturation has been raised far beyond its normal threshold value; and when the hemoglobin is very high, as in marked polycythemia, a considerably lower content of reduced hemoglobin will result in the appearance of cyanosis. Lundsgaard and Van Slyke's work has been of great value in the problem of congenital cyanosis in distinguishing the essential causative factors from the modifying ones, and by the graphic presentment of their relative threshold values and combined significance. The modern theory of morbus caeruleus as recognized by Abbott in her chapter on Congenital Cardiac Disease in the last edition of Osler's Modern Medicine combines the essential principles of both the old theories of Senac and Morgagni. The oxygen-unsaturation of the capillary blood corresponds to the mixture of venous and arterial blood of the Senac

theory, while the marked filling of the capillaries corresponds to the Morgagni view that the cyanosis is peripheral. Abbott fails, however, to recognize sufficiently the important recent work on capillary morphology and pathology bearing directly upon the question of morbus caeruleus, just as Lundsgaard and Van Slyke have failed in recognizing the significance of the morphologic capillary picture in cyanosis. The histologic study of the capillary dilatation in morbus caeruleus has been made by Chouppe, Varict and Gamfert, and the study of the same condition by means of the capillary microscope has been carried out by Janzen, Rominger, Frontali and Redisch and Rösler. LeBlanc has demonstrated that for the appearance of cyanosis in the skin or mucous membranes the thickness of the blood layer in the capillaries is an essential factor. In normal capillary width blood rich in reduced hemoglobin appears still red, but in dilated capillaries blood poor in reduced hemoglobin appears blue. Redisch and Rösler find the capillary-microscopic picture specific for the morbus caeruleus. Paraphrasing their description, on a dark-red background arranged in many layers the capillary loops appear very large as a whole, but especially thickened at their curves and in the venous arm of the loop. The capillaries are many times interwound but less tortuous. In a striking number of the capillaries there is stasis, in others a corpuscular stasis with slightly slowed current. In the upper layers especially there are fine, less drawn-out, scarcely wound loops, which are interpreted as newly-formed capillaries. There exists, therefore, according to the capillary microscope a condition of the most marked capillary hyperemia with especial involvement of the venous limb of the capillary, with a tendency to stasis of the capillary circulation and the formation of new capillaries. This picture stands out well differentiated from that of the capillaries in cases of cardiac decompensation. There is found in morbus caeruleus and only in it the capillary picture described above. In common with Pachioni, Redisch and Rösler believe that this capillary condition is the chief cause of the extreme cyanosis of morbus caeruleus; it is specific for this condition but it is to be regarded as a secondary symptom of severe congenital cardiac lesions. It is easily diagnosed in life, and may best be designated as "congenital capillary dilatation". Two questions naturally arise in connection with the specific capillary picture of morbus caeruleus, its relationship to the occurrence of drumstick toes and fingers, and to the problem of cyanosis in general. In eight cases of morbus caeruleus with typical capillary picture and cyanosis of high degree, drumstick fingers and toes were present in all; in five other cases of drumstick fingers there occurred four times the capillary picture of cardiac decompensation and in one case a normal capillary picture. It is, therefore, evident that drumstick fingers and toes do not possess a characteristic capillary picture. Pachioni is really the father of the idea that the chief factor of the cyanosis in congenital cardiac lesions is the *congenital capillary dilatation.*

Through the abnormal cardiac function of the fetus, with the resulting stasis, there occurs a disturbance of development in the most distant capillaries showing a fetal structure. No changes in the capillary circulation are to be expected in septal defects owing to the equal pressure in the two ventricles. Still less will they occur in open ductus Botalli, which represents the normal fetal circulation. The occurrence of cyanosis in these cases present no specific capillary picture, but only that of cardiac decompensation. Pachioni also believes that the cases of "cyanose tardive" can also be explained by his theory. If in extrauterine life the circulatory difficulty becomes lessened or disappears, the conditions for the abnormal capillary dilatation are still present, and there arises a condition of latency. Pachioni does not exclude the possibility that after birth changes occurring in the capillaries of the skin may lead to cyanosis. Further, after birth the already prepared capillary accommodation may become greatly increased. The organism has three possibilities of compensation for the circulatory difficulties attending congenital cardiac lesions, the dilatation of the developing capillaries, the new-formation of capillaries and the increase of the canals of Hunter (intercapillary anastomoses). The accommodation capacity of the capillaries lasts throughout early childhood, even up to puberty. This point of view is also of great significance in regard to cyanose tardive. Should the accommodation capacity of the capillaries become insufficient there will take place stasis and blocking of the capillaries leading to the production of the picture of morbus caeruleus. In this connection the increased circulatory demands and the increase of venous pressure due to the erect position of the body, especially in the extremities of the body, and the essentially increased difficulty of emptying the capillaries towards the venous limb must play an important rôle in the production of a delayed cyanosis. According to Redisch and Rösler, Weiss and Löwbeer, morbus caeruleus cannot be explained on the ground of a quantitatively increased cyanosis, as held by Lundsgaard and Van Slyke. According to Redisch and Rösler no case of morbus caeruleus occurs without the characteristic capillary picture described above—that is dilatation of the venous limb and slowing of the stream. Redisch and Rösler have also been the first to describe a characteristic capillary picture occurring in two cases of stenosis of the isthmus of the aorta. The capillaries of the upper extremities were lengthened, and the venous limb greatly dilated, and the current slow. At the elbows there were multiple capillary aneurysms. The capillaries of the lower extremities, on the other hand, were exceedingly fine and delicate without aneurysmal dilatations. In isthmus stenosis of the aorta there is a marked difference in blood pressure between the upper and lower halves of the body. In the two cases described the blood pressure in the lower extremities was definitely below normal. Whether the total mass of blood in the lower extremities was less than that in the upper could not be determined. In

both cases the legs were well developed and functionally capable; there was no evidence of claudication, in spite of their paleness and coolness. The condition of the capillaries is only the expression of the relative anemia of the legs and lowered blood pressure due to the aortic stenosis. The question of the multiple formation of capillary aneurysms in the upper extremities is an interesting one, since as a rule they are regarded as an affection involving the whole vascular system, due to a vasoneurotic diathesis, lues, atherosclerosis or other severe vascular lesion. Redisch and Rösler have greatly advanced the use of the capillary microscope in the study of circulatory disturbances by their observations. An entirely new aspect is given to morbus caeruleus by their findings of a constant capillary dilatation which they conceive to be the cause of the affection, and by their demonstration that it stands in no relationship to the production of drumstick fingers. The capillary picture discovered by them in isthmus stenosis of the aorta will prove to be a valuable diagnostic sign, if confirmed.

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## *THE BOSTON MEETING*

The most successful Clinical Week ever held by the College was that just closed in Boston. With a registration running in the neighborhood of fifteen hundred there was a remarkably full attendance at each session, even up to the last one. The program for the afternoon and evening meetings presented a rich variety of timely and interesting subjects, and was carried through in an eminently business-like manner. Much praise was heard of the clinical presentations, and for once the clinics may be said to have measured up fully to the expectations of the visiting Fellows and Associates. The arrangements at the Statler Hotel were ideal, and the College owes its thanks to the Management for such efficient cooperation. There was not a single slip-up. The Annual Dinner was most successful, the Ball Room being filled to capacity, and the guests were greatly entertained by the amusing characteristic speech given by Dr. Vincent. An unusually large number of Fellows and Associates were inducted into the College at the Convocation. The impression given by this meeting was that the College has fully arrived, that it has become a great institution in the medical forces of this country, and that it can go on now fully established and entrenched in its work and purpose to the greatest success and accomplishments. It has shown that it fills a definite place among the medical societies of the country, that it occupies a unique position in service and function, and that as a factor in the post graduate medical education of the internist it occupies the highest place No one attending this meeting can have the slightest doubt of the tremendous success achieved by the College. The character of the membership as constituting the most representative internists of the country is very impressive. To the out-going President, Dr. C. F. Martin, of Montreal, is due the sincere thanks of the organization for his labors in advancing the aims of the College. Filled with the highest ideals of what the College should stand for, and what it

should represent, he has during his term of office done much to perfect its organization. The College is also greatly indebted to the Boston physicians who contributed so much to the success of this meeting, and particularly to their most efficient General Chairman, Dr. James H. Means, whose untiring energy played a very great part in the accomplishment of the most perfect Clinical Week the College has yet seen.

# Abstracts

*Hemorrhagic Glomerular Lesions Produced by Filtrates of Streptococcus Viridans Cultures.* By Arnold R. Rich, John H. Bumstead and Martin Frobisher, Jr. (Proc. of the Soc. for Exper. Biology and Med., February, 1929, p. 397).

It is well known that hemorrhagic glomerulonephritis occurs with great frequency in association with *Streptococcus viridans* infections, especially with endocarditis caused by this organism. The glomerular changes in the latter affection are generally regarded as a direct result of damage caused by minute emboli from the vegetations on the heart valves. This explanation was doubted by the workers named above for the following reason: If the nephritis associated with *Streptococcus viridans* endocarditis is merely the result of emboli, one might reasonably expect to encounter a similar nephritis quite as commonly in every form of endocarditis characterized by profuse, friable vegetations, regardless of the etiology. But this is not the case. There is no relation between the size of the valvular vegetations and the occurrence or degree of nephritis. The writers have observed florid hemorrhagic nephritis in association with gonococcal endocarditis, in which the vegetations were confined to the right side of the heart, and in which therefore the capillary bed of the lungs would act as a filter for emboli escaping from the vegetations. It may be remarked that gonococcal endocarditis resembles *Streptococcus viridans* endocarditis in the extraordinary frequency with which it is accompanied by hemorrhagic nephritis. A microscopic study failed to convince that the damage to glomerular tufts in the nephritis associated with *Str. viridans* endocarditis is necessarily dependent upon the presence of emboli. The glomerular damage differs in no way from that observed in cases of nephritis in which emboli could have played no rôle. It seemed possible that the high incidence of nephritis occurring in association with certain forms of bacterial endocarditis might be referable to the action of toxins produced by the microorganisms in question, rather than to emboli. Experiments were, therefore, carried out with a strain of *Str. viridans* obtained from the blood of a patient suffering from a typical subacute endocarditis with evidences of renal involvement. They were able to produce glomerular damage in rabbits by the intravenous injection of bacteria-free filtrates of fresh broth cultures of this organism. The sterility of the filtrates was always proven by culture. The amount of filtrate injected varied between 2 and 20 cc., and the animals were killed on the day following the injection. There was no definite relation between the amount injected and the degree of renal injury produced. Some unexplained individual susceptibility played a greater rôle. Realizing the sources of error involved in the interpretation of apparent cellular alterations in the glomerular tuft, they regarded as positive only these cases in which actual hemorrhages occurred into Bowman's capsule and the convoluted tubules. The hemorrhages visible at autopsy in the gross varied in number from only one or two to a profuse peppering of the cortex of each kidney. Microscopically, the hemorrhages were always in Bowman's capsule or the tubules, never in the interstitial tissue, and in all instances the escaped blood was perfectly fresh in appearance. In no case did the control injections of broth alone affect the kidney. Spontaneous hemorrhagic glomerulo-nephritis in the rabbit is mentioned extremely rarely in the literature. The investigators have never encountered it in the study of the kidneys of hundreds of rabbits killed for other purposes during the past several years, and their control series of 9 rabbits were free from it. They feel, therefore, convinced that the present experiments demonstrate clearly that, in the Berkefeld filtrates of broth cultures of a patho-

genic strain of *Streptococcus viridans* there is something which can produce glomerular damage in the rabbit. As far as they are aware this is the first time that a condition comparable to acute hemorrhagic glomerulonephritis has been produced experimentally by means of a bacterial filtrate. Whether they are dealing with a true toxin cannot yet be stated. There is evidence, however, that the renal damage in their experiments has nothing to do with allergy. Efforts to concentrate the toxic principle of the filtrate, and so to obtain, possible, a higher percentage of instances of renal involvement have not yet been successful. No explanation can be offered for the differences in individual susceptibility to the injurious substance in these experiments. In a limited number of experiments in which filtrates of cultures of other bacteria were injected, no renal changes were produced.

*The Experimental Transmission of Leukemia in Mice.* By Maurice N. Richter and E. C. MacDowell (Trans. Soc. for Exper. Biol. and Med., February, 1929, p. 362).

The only report in the literature of the successful transmission of leukemia in mammals is that of Snijders, who succeeded in transmitting the disease by the inoculation of emulsions of tissues from spontaneously affected guinea pigs into normal animals of the same species. Unsuccessful attempts to transmit leukemia in mice were made by Haaland and Tyzzer. In a strain of mice designated as C58, which had been inbred by brother-sister matings since 1921, it was observed that a considerable number of those that lived more than 8 months had enlargements of their spleens and lymph nodes, which on microscopic examination were shown to be due to lymphatic leukemia. Tumors other than those occurring as part of the leukemic symptoms are uncommon in this strain. Saline emulsions of spleens from 6 mice spontaneously affected with lymphatic leukemia were inoculated intraperitoneally and subcutaneously into non-leukemic mice from the same and also from other strains. The non-leukemic mice were young animals of both sexes, from 1 to 2 months old. Following inoculation there appeared in each of the 6 experimental animals enlarged lymph nodes and spleens, with masses or nodules of lymphoid tissue in the abdominal cavity, sometimes forming large tumor-like growths in the mesentery, around the kidneys or along the genital tract. Subcutaneous nodules, enlargements of superficial lymph nodes, mediastinal growths, and fluid in the peritoneal or pleural cavities were also frequently observed. Microscopically, these growths consist of lymphoid cells in a delicate stroma. Many cells are in mitosis and there is infiltration of surrounding structures. Infiltration of the liver, pancreas or lung is common. In some of the inoculated mice there was a striking increase in the number of circulating white corpuscles. The highest count recorded in the experiments was 262,000 per cm., about 3 weeks after inoculation. The increase in cells was due to an absolute and relative increase in the number of lymphocytes, many of which were immature. In some instances, small numbers of abnormal cells were observed in the blood even when the total white count was normal. Similar changes have resulted from the inoculation of emulsions of these experimentally produced lymphoid enlargements, and the condition has been successfully transmitted through several experimental passages. One line has now reached the sixth transfer. Of 110 mice of strain C58 that lived more than 10 days after inoculation, 36 are still alive, and 74 have died or been killed. Of the latter, transmission was successful in 56, unsuccessful in 10, while diagnosis is not yet complete in 8. Fourteen animals of other strains which lived more than 4 days after inoculation with the same material, have had neither lymphatic enlargements nor leukemic blood pictures. Thirteen are still alive, one died but presented no lesions resembling leukemia.

*Studien über der Arteriellen Tiefdruck (Hypotonie). Zur Frage der Beziehung zwischen Blutzuckerspiegel und Blutdruckwert.* By. Dr. Franz Kisch, (Klin. Wochenschr., 26 February, 1929, p. 400). That there exists a relationship between hyper-

glycemia and hypotonia has been the subject of much discussion. Observations by Joslin indicate that in diabetics over 35 years of age the blood pressure is higher than in normal individuals. With this Hitzenberger agrees, placing the percentage of cases of high blood pressure among diabetics as 46 per cent. Maranon also is of the opinion that diabetics are more inclined to high blood pressure than non-diabetics of the same age. Kylin estimates the number of cases of hypertonia among diabetics as 39 per cent; Rosenbloom at 22 per cent; Persei at about 25 per cent; Strauss at 33 per cent. Ernst Wiechmann estimated the blood pressure in 256 diabetics and found a higher per cent of cases with high blood pressure than in normal cases. Rosenbloom found high blood pressure in diabetics only in cases complicated with aortitis, arteriosclerosis, nephritis, cardiac hypertrophy or aortic insufficiency. Barach found high blood pressure only in those diabetics who had at the same time arteriosclerosis or nephritis. Koopman affirms that young diabetics show a normal blood pressure, while in older patients high blood pressure is the rule. A. Friedländer, on the other hand, holds that diabetes scarcely influences the blood pressure. Kisch studied the blood pressure in 463 diabetics (292 males, 171 females) in the age-limits of 20-80 years. In 136 cases a hypertonia was found (blood pressure over 140 mm. Hg.), 29.4 per cent. In 65 of these 136 diabetics ketonuria was present, 47.7 per cent. A similar study made of 1800 non-diabetics in the same age-limit, 20-80 years (1055 males, 745 females), showed a high blood pressure (over 140 mm. Hg.) in 616 cases, that is in 34.3 per cent. A comparison as to the incidence of hypertonia in diabetics and non-diabetics, showed it to be present in 29.4 per cent of the former as compared to 34.3 per cent in the latter; thus the number of cases of hypertonia among diabetics was 4.9 per cent less than among non-diabetics. The occurrence of low blood pressures among diabetics was first shown by Hitzenberger, who found that the blood pressure in young diabetics was considerably lower in a greater percentage than in non-diabetics of the same age. As the cause of the low blood pressure he assumed that it was dependent upon the accompanying acidosis, since the blood pressure rose when this was lessened or disappeared. Joslin also states that the blood pressure in diabetics under 25 years is usually below normal. Barach noted in these cases of diabetes in which the pressure was low that there was a marked emaciation or general body weakness. Wiechmann found a hypotonia in 26 per cent of male diabetics under 30 years of age; and according to the statistics of J. Barach 37 per cent of diabetics have a low blood pressure (under 110 mm. Hg.). Kisch found in his 463 diabetics 58 cases in which the arterial blood pressure was 100 mm. Hg. and lower, that is, in 12.5 per cent. In 30 of these 58 cases with arterial hypotonia there was a concomitant ketonuria. In the 1800 non-diabetics (1055 males, 745 females) there were 265 with a low arterial pressure, that is, 14.7 per cent. Comparison of the number of hypotonic cases in diabetes with the number in non-diabetic cases, there were 12.5 per cent of the former in contrast to 14.7 per cent in the second group. Comparing the blood pressure curves with the blood sugar curves he found that neither in diabetics or in non-diabetics, be the blood pressure high or normal, was there any increase in blood pressure at the time of the greatest height in blood sugar. He, therefore, concludes that hyperglycemia as such is without influence upon the blood pressure; that with the highest, medium and moderate degrees of hyperglycemia, the percentage of diabetics with normal blood pressure remains about the same. Neither in diabetics or in non-diabetics is there any conformity between the blood pressure and blood sugar curves. In 16-19 per cent of cases of completely de-sugared diabetics a lowering of blood pressure occurs at the time of complete aglycemia, probably as the result of the fasting condition. Insulin treatment is, therefore, without significance in its effect upon the blood pressure. As far as ketonuria is concerned in the question of high or low blood pressure, 47.7 per cent of the diabetics with arterial hypertension and 51.7 per cent of diabetics with arterial hypotension showed ketonuria, a practically equal relationship showing that there is no essential relationship between ketonuria and the conditions of blood pressure.

# Reviews

*Tumors Arising from the Blood Vessels of the Brain. Angiomatous Malformations and Hemangioblastomas.* By Harvey Cushing, Professor of Surgery, Harvard Medical School and Surgeon-in-Chief, The Peter Bent Brigham Hospital, Boston; and Percipal Bailey, Formerly Associate in Surgery, The Peter Bent Brigham Hospital and Associate Professor of Surgery, University of Chicago. 219 pages, 150 illustrations. Charles C. Thomas, Springfield, Illinois and Baltimore, Maryland, 1928. Price in cloth. $7.50.

This is a clinicopathological study in which experimentation plays no part. The pathological specimens on which it is based have been in process of collection over a period of nearly twenty-five years. It was begun at the Johns Hopkins Hospital and has been continued at the Peter Bent Brigham Hospital. Although in Cushing's experience the hemangiomas of the brain are in proportion to other intracranial tumors as only two to one hundred, the clearing up of some of the obscurities of a minor group of tumors may sometimes indirectly throw unexpected light on the whole. The book treats in Part I of the angiomatous malformations, angioma venosum and angioma arteriale, which together are illustrated by fourteen cases. There follows the case reports a general discussion of the symptomatology, pathology and treatment of the various forms. Part II treats of the cerebellar hemangioblastomas, illustrating them by eleven cases, with a discussion of symptomatology, pathology and treatment. This is followed by a short discussion of cerebral hemangioblastomas. This is an interesting little monograph based upon a relatively small number of cases, studied in connection with the literature. It will make an especial appeal to the pathologist and brain surgeon. A specially valuable feature of the case reports are the controlled records of the cases. The book is excellently printed, and the illustrations unusually good. The bibliography is also a valuable feature of the book.

*Racial Hygiene.* A Practical Discussion of Eugenics and Race Culture. By Thurman B. Rice, A.M., M.D., Associate Professor of Bacteriology and Public Health, Indiana University School of Medicine; Extension Lecturer in Eugenics, Indiana University; Chairman Indiana Eugenics Committee. 376 pages, 58 figures. The MacMillan Company, New York, 1929. Price in cloth: $4.50.

The plan of this book is to present the fundamentals of genetics, the science of heredity in the earlier chapters, in order that the biological foundation may be laid for the sociologic application to be made in the succeding chapters. The importance of the biologic basis for eugenics and for the understanding of sociology, of social work, of educational systems, of disease, delinquency, degeneracy, crime, pauperism and mental defectiveness is being more and more appreciated. Much effort has been put forth to make the biologic basis accurate according to the latest scientific verdict. For the most part subjects still in controversy are avoided or handled in the manner that seems most likely to avoid unnecessary confusion. It is not intended that the opinions expressed in regard to various social problems shall be regarded as final since there is room for wide divergence of opinion on all such matters, but the author insists that the basis of a great number of perplexing social problems is biological. If the cause of an antisocial condition is found in a biologic relation, then it seems reasonable that the logical remedy is the correction of the cause, if this is possible. It seems absurd to attempt to correct such a condition with education, religion, philanthropy, psychology or any other

of the thousand and one remedies which have been recommended. The author believes that eugenics constitutes a biologic problem with sociologic implications. The reader is reminded that the welfare of the race rather than that of the individual is the aim of this book; but that the welfare of the race will ultimately mean the greatest good to the greatest number of individuals. The author hopes that the matter presented will be found interesting as well as instructive, and that it may not be adjudged impractical ultimately because it cannot be applied immediately. It may be generations before an adequate program can be evolved. But even so it is better that eugenics grow into its proper place slowly rather than prematurely. The education of thinking people in the principles of race culture and hygiene is the first and most important step in the preparation of the soil. The book presents the basic facts of genetics and eugenics in simple and understandable language, which may be easily understood by any intelligent reader. The laws of heredity are made clear to the layman. It is the most practical book on eugenics that has yet been written, and as such may be warmly recommended to all readers. It cannot fail to accomplish a most useful end in making intelligible to the layman the laws of heredity and reproduction.

*Gould's New Medical Dictionary*, Containing All the Words and Phrases Generally Used in Medicine and the Allied Sciences, With Their Proper Pronunciation, Derivation and Definition. Based on Recent Medical Literature. By George M. Gould, A.M., M.D.; Edited by R. J. E. Scott, M.A., B.C.L., M.D., Fellow of the New York Academy of Medicine. Second Edition Revised and Enlarged. 1522 pages, with numerous illustrations and 170 tables, Including a new one of micro-organisms, comprising 68 pages, by D. H. Bergey, M.D., Professor of Hygiene and Bacteriology, University of Pennsylvania. P. Blakiston's Son and Company, Philadelphia, 1929. Price in cloth: $7.00, with thumb index: $7.50.

The first of Dr. George M. Gould's medical dictionaries was published in 1890, under the title of "A New Medical Dictionary". Two years later "A Pocket Medical Dictionary" of 12,000 words was published, and this was followed, in 1894, by his monumental work "An Illustrated Dictionary of Medicine, Biology and Allied Sciences" the current edition (6th) of which comprises 1700 double columned pages. Ten years later, a supplement to the Illustrated Dictionary, containing 38,000 words was published under the title of "A Dictionary of New Medical Terms". The title of the first dictionary, namely, "A New Medical Dictionary" was in a later revision changed to "The Student's Medical Dictionary" which contained a much larger vocabulary. Under this title the book was continued with revisions until 1906, when it gave place to a new and larger issue entitled "The Practitioner's Medical Dictionary" which has served the profession for a number of years, and may still continue to do so. We come now to the present issue "Gould's Medical Dictionary", which may be said to be the sum of all of Gould's dictionaries. The important features of this new and latest dictionary are: the larger and bolder type, the additional pictures, the increase in size of the volume, the added biographical detail, and many new abbreviations now employed in current medical literature. It contains about 76,000 words, hundreds of which are new terms. Other new features are a physician's and a veterinary dose table, based on the U. S. P., X, a diet table and a table of micro-organisms by Dr. D. H. Bergey. The interests and needs of the busy practitioner and the active general medical reader have been kept in mind. No matter has been inserted that is not appropriate, and few pictures are included that are in the most commonly used text and reference books. Eponymic terms are in their proper alphabetical order, so that one no longer need be in doubt whether to look under test, reaction, phenomenon, syndrome, sign or symptoms, etc., for the information sought. The tabulation and systematic classification of other correlated terms, established in usefulness, have been continued. The spelling conforms to the standard requirements, and the definitions are based

upon the standard literature and authoritative textbooks of the day, and are not copies from the older vocabularies. The pronunciation is clearly shown by a phonetic arrangement of letters. The original alphabetical sound of the letter is the key. Only when there may be any doubt has the pronunciation been indicated by a diacritic mark. Proper names and their derivations only have been capitalized in the titlewords, in accord with present usage. The constant aim of the publisher and editor has been to make this new dictionary more accurate, more comprehensive and more helpful. Over 706,000 volumes of Gould's Medical Dictionaries have been distributed over the world, a fact that attests their intrinsic value. This dictionary will be found most practical and serviceable. It shows a high standard of accuracy, and is brought up to date as fully as any dictionary may hope to be. In checking over the newer terms the reviewer notices the absence of "blastophthoria," "cyclostage," and a number of the most recent terms used in modern bacteriology. Just why "blastophthoria" should have escaped the editor it is difficult to see, for this term is one of the most commonly used in the medical genetics of the present time. The definition of "disassociation" makes no reference to its usage in bacteriology. "Dysontogenesis" is another important common term of pathology which is wanting, as is also the bacteriologic term "tropin," and the genetic term "linkage." The deficiencies of this dictionary are most prominent in the terminology of modern pathology, bacteriology and genetics. Nevertheless it is a most useful and valuable book, especially fitted for the needs of the medical student and practitioner. The definitions are for the chief part excellent and terse. It is the best of all the medical dictionaries published in the English language, and for this reason it is highly recommended.

*An Atlas of Human Anatomy.* For Students and Physicians. By Carl Toldt, M.D., Assisted by Professor Alois Dalla Rosa, M.D., Adapted to English and American and International Terminology, by M. Eden Paul, M.D., Brux., M.R.C.S., F.R.C.P. New Second Edition. Volume I, Containing Sections on Regions of Human Body—Osteology—Arthrology—Myology (Figures 1-640 and General Index). Volume II, Containing Sections on Splanchnology—Angeiology—Neurology—Organs of the Senses (Figures 641-1505, with Appendices and General Index to the two volumes). The MacMillan Company, New York, 1928. Price in cloth, $20.00.

This new second edition of the Toldt Atlas of Human Anatomy has been revised and corrected, and in its present form constitutes the most complete and best of the various atlases on human anatomy that has yet been offered. The illustrations are excellent, and are especially noteworthy for their accuracy and simplicity. There is no descriptive text, but the figures present so well what they are intended to do, and the parts are so well labelled, that the book reveals the various anatomical structures and their relationships as clearly as in an actual dissection of the given part. Both the American and International terminologies are given. The two volumes are an invaluable aid to the medical student of anatomy, and should be in the hands of every one during his dissection of the human subject. Further, for the purpose of a quick refreshing of one's anatomical memory this atlas is most serviceable. It can be highly recommended to both the medical student and the surgical practitioner.

*The Blood Plasma in Health and Disease.* By J. W. Pickering, D.Sc. (Lond.), Lesturer on Hematology, University of London, King's College. Monographs of Medical and Surgical Science, Edited by R. J. S. McDonald, D.Sc., M.D., F.R.C.P. (Edin.), University of London, King's College. 247 pages. The MacMillan Company, New Yorfl, 1928 Price in cloth: $4.25.

The object of this series of monographs is to provide a medium by which the knowledge they have collected may become generally available. It is intended that so far as possible the monographs should be of

value not only to the research worker, but, by the avoidance of undue technical detail in the applied chapters, that they should also be of practical use to the clinician. Blood plasma has been investigated from the standpoint of bio-chemistry, physiology and pathology. Each of these branches of research has revealed important truths, but the differences of outlook among workers have often led to the treatment of this subject in compartments. An attempt will be made in the limits of this small volume to correlate certain facts derived from each of these sources of information, and to point out some of their practical applications. Evidence will be collated which suggests that the plasma is of fundamental importance in the life of the whole body, and it will be shown that morbid conditions appear when the stability of plasma is altered. Modern knowledge of the plasma is largely derived from the investigation of the precipitability and coagulability of that fluid. Following a historical introduction, the various chapters treat in succession of: the protein of blood plasma in fractions and as a whole; fibrinogen; the inception of blood clotting; the stabilization of blood plasma; thrombosis and antithrombosis; fibrin; the suppression of the coagulability of the blood in vivo; the condition of the blood in anaphylactic and anaphylactoid states; current theories of blood coagulation; the arrest of hemorrhage; the problem of thrombosis; menstrual and puerperal blood; and the blood of abnormal bleeders. Following these are three appendices on: Synapsis of the newer hemostatics; general bibliography and the bibliography of methods of extracting fibrin. This volume sums up what is known of the blood plasma in health and disease. Particularly important is the critical discussion of our present knowledge on coagulation of the blood and thrombosis, and on congenital hemophilia. It is an important book for the medical student, laboratory worker and for the practitioner as well. It contains much information of practical value to the practising physician in its discussion of bleeding and its treatment.

JOHN HERR MUSSER, M.D.,
President, American College of Physicians, 1929-30
(1551 Canal Street, New Orleans, La.)

# College News Notes

During the Thirteenth Annual Clinical Session of the American College of Physicians at Boston, April 8-12, Dr. John Herr Musser was inducted as President of the American College of Physicians for the succeeding year, having been elected President-Elect at the Twelfth Annual Clinical Session at New Orleans in March, 1928.

Dr. Musser was born in Philadelphia, June 9, 1883, received his Baccalaureate Degree at the University of Pennsylvania in 1905 and his Medical Degree at the same institution in 1908. He is the sixth Musser physician in direct descent from the original one who came over to this country in the early part of the eighteenth century. He was Assistant Physician to the Presbyterian Hospital, Philadelphia, 1912-24, Physician to the Philadelphia General Hospital, 1914-24, Physician to the Howard Hospital, Philadelphia, 1919-24, and Assistant Professor of Medicine at the University of Pennsylvania Medical School, 1919-24. From 1911 to 1920, he was Assistant Editor of the American Journal of Medical Sciences, and from 1920 to 1924, Editor of the same Journal, which is the oldest medical journal in the United States. Dr. Musser terminated his Philadelphia appointments in 1924 to become Professor of Medicine at Tulane University of Louisiana, School of Medicine, New Orleans, which appointment he still holds. He is Physician to the New Orleans Charity Hospital and Editor of the New Orleans Medical and Surgical Journal. During the World War, he was successively commissioned Lieutenant, Captain and Major, in charge of the Medical Service of the University of Pennsylvania Base Hospital, No. 20, A. E. F. He is now Lieutenant-Colonel in the Medical Reserve Corps.

Dr. Musser is a member of the Psi Upsilon and the Alpha Mu Pi Omega fraternities. He is a member of the Orleans Parish Medical Society, the Louisiana State Medical Society, a Fellow of the American Medical Association, member of the American Climatological and Clinical Association, member of the Society for Experimental Biology and Medicine, member of the American Society for Clinical Investigation, member of the Association of American Physicians, member of the Southern Medical Association, and has been a Fellow of the American College of Physicians since June 20, 1920. He has served on various important committees, and has been a member of the Board of Regents of the College for several years. As General Chairman of the New Orleans Clinical Session of the College in 1928, he distinguished himself as an organizer of unusual ability, and displayed those qualities which contribute greatly to co-operation, efficiency, high standards and cordiality.

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Dr. Grafton Tyler Brown (Fellow), Washington, D. C., has been reappointed Chairman of the Membership Committee of the Medical Society of the District of Columbia.

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Dr. Robert M. Moore (Fellow), Indianapolis, Indiana, addressed the Summitt County Medical Society at Akron, Ohio, February 5. His subject was "Some Considerations in Heart Failure of the Anginal Type."

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Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa., addressed a Postgraduate audience in the historic Clinical Amphitheatre of the University of Maryland, Baltimore, on January 31; his subject being "Emphysema and its Complications."

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Dr. Alfred W. Gray (Fellow), Dr. C. H. Stoddard (Fellow) and Dr. R. W. Blumenthal (Fellow) are all members of

the Board of Directors of the Medical Society of Milwaukee County, Milwaukee, Wisconsin.

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Dr. F. C. Potter (Fellow), Akron, Ohio, is President of the Summitt County (Ohio) Medical Society for 1929, and Chairman of the Medical Committee of the Red Cross Disaster Relief, Summitt County Chapter.

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Dr. William C. Voorsanger (Fellow), San Francisco, is Medical Director of The Oaks Sanitarium, Los Gatos. The Oaks Sanitarium celebrated its fifteenth birthday during the week, February 15-22. This is an institution for the treatment of Tuberculosis and allied pulmonary conditions.

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Dr. Harry M. Hall (Fellow), Wheeling, West Virginia, published an article entitled "Relation of the Hospital Staff to the Directorate and Superintendent" in the February Issue of the West Virginia Medical Journal and also in the February Issue of Hospital Management. Dr. Hall is President of the West Virginia State Medical Association.

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Dr. Lee Rice (Fellow), San Antonio, Texas, is a Governor for Texas of the Gorgas Memorial. At the last meeting of the Southern Medical Association in Asheville, he was elected Chairman of the Medical Section. Under the direction of the Gorgas Memorial Institute, which is organized to perpetuate the life work of the late Major-General Gorgas in preventing unnecessary illness, Dr. Lee Rice has contributed a number of articles, which have had wide circulation. Among these are "Heart Disease" and "Preparation for Inevitable Heart Disease Made by Combination of Infection and Overstrain."

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Dr. Louise Tayler-Jones (Fellow), Washington, D. C., attended the Medical Women's National Association meeting at Paris, April 11-13.

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In the January Issue of the Southern Medical Journal, the following articles were contributed by Fellows of the College:

"The Promotion of the Common Welfare: The Aim of Modern Medicine," by William R. Bathurst, Little Rock, Ark.

"Is Malignant Hypertension a Disease Entity?" by J. B. McElroy, Memphis, Tenn.

"Relation of Medical Education to the Public," by Stuart Graves, University, Ala.

"A Decade of Transition in American Psychiatry," by W. E. Gardner, Louisville, Ky.

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The following Fellows appeared on the Program of the 45th Annual Convention of the Tri-States Medical Association of Mississippi, Arkansas and Tennessee at Memphis, February 6-8:

Dr. R. H. Balyeat, Oklahoma City.
Dr. Frank Smithies, Chicago.
Dr. L. G. Rowntree, Rochester, Minn.
Dr. John H. Musser, New Orleans.
Dr. Lawrason Brown, Saranac Lake.

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Dr. C. Lydon Harrell (Associate), Norfolk, Virginia, addressed the Warwick County Medical Society, January 28, on "Calcium Deficiency in Disease."

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Dr. Sinclair Luton (Fellow), St. Louis, Missouri, was a guest of the Jackson County (Illinois) Medical Society at its annual meeting in Carbondale, Illinois, December 20, 1928. Dr. Luton addressed the meeting on "Diseases of the Heart."

Dr. Luton addressed the Frisco System Medical Association's annual meeting at Pensacola, Fla., October 22-23, 1928, on "The Diagnosis of Chronic Heart Disease."

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Dr. Linn J. Boyd (Fellow), New York, N. Y., is author of an article in the January Issue of the Journal of the American Institute of Homeopathy, entitled "The Necessity for a Scientific Concept of Homeopathy."

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Dr. Carl V. Vischer (Fellow), Philadelphia, Pa., Associate of Devitt's Camp for the treatment of Pulmonary Tuberculosis, is author of an article in the January number of the Journal of the American Institute of Homeopathy, entitled "Ultra Violet

Ray in the treatment of Pulmonary Tuberculosis," with case reports.

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Dr. James M. Anders (Master), Philadelphia, Pa., addressed the association of College Presidents of Pennsylvania on the "Research Method of Teaching Science," November 24, 1928, at Harrisburg.

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Dr. Donald R. Ferguson (Fellow), Philadelphia, Pa., was recently elected Chairman of the Bureau of Clinical Medicine of the American Institute of Homeopathy.

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Dr. Linn J. Boyd (Fellow), New York, N. Y., sailed for Europe on December 22 for a series of personal conferences with the Homeopathic Leaders of England, Belgium, Holland, Germany, Italy, Spain, Switzerland and France, in preparation for the European reception of the 1929 International Committee of the American Institute of Homeopathy which will sail for Europe on June 27, 1929.

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Dr. Linn J. Boyd (Fellow), of the New York Homeopathic Medical College has been conducting extensive "Drug Proving" experiments with the aid of a "Proving Squad" consisting of medical students of the College. Dr. Boyd is also Chairman of the Bureau of Drug Pathogenesis of the American Institute of Homeopathy.

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Dr. Carl V. Vischer (Fellow), Philadelphia, Pa., is author of another article on the Treatment of Tuberculosis which appeared in the January number of the Hahnemannian Monthly entitled "Management of the Chronic Tuberculous Patient."

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Dr. Albert D. Foster (Fellow), formerly stationed at the U. S. Marine Hospital at Boston, Chelsea, Massachusetts, where he is Medical Officer in Charge.

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Dr. Lester L. Powell (Associate), Portland, Maine, has been elected President of the Portland Medical Club for the year 1929. Dr. Eugene H. Drake (Associate) was the retiring president.

Dr. William Thalhimer (Fellow), formerly Director of the Laboratory of Pathology of Columbia Hospital, Milwaukee, Wisconsin, accepted on February 1 the appointment of Director of Laboratories of the Michael Reese Hospital, of Chicago. Dr. Thalhimer's new address is: The Nelson Morris Institute, 29th and Ellis Avenues, Chicago, Illinois.

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Dr. Thomas J. Burrage (Associate) was appointed Chairman and administrative head of the emergency staff organized in Portland, Maine, for relief against influenza or an epidemic of any other nature, recently organized by the Portland Chapter of the American Red Cross. Dr. Lester L. Powell (Associate) was appointed Director of the Immanuel Baptist Parish House Hospital, with a capacity of more than 250 cots, in connection with the same organization.

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Dr. George G. Hunter (Associate), Los Angeles, Calif., has been elected President of the Los Angeles County Medical Association for 1929, and Secretary-Treasurer of the Los Angeles Clinical and Pathological Society.

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The following appointments on the faculty of the University of Oregon Medical School were published recently in *Northwest Medicine*:

Dr. Noble W. Jones, Clinical Professor of Medicine.

Dr. T. Homer Coffen, Clinical Professor of Medicine.

Dr. Harold C. Bean, Assistant Clinical Professor of Medicine.

Dr. Ralph C. Matson, Associate Clinical Professor of Medicine.

Dr. James Marr Bisaillon, Assistant Clinical Professor of Medicine.

Dr. Isidor C. Brill, Assistant Clinical Professor of Medicine.

Dr. Charles E. Sears, Assistant Clinical Profesor of Medicine.

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Dr. George H. Hoxie (Fellow), Kansas City, Missouri, was recently appointed a member of the Jackson County Medical Society Cardiac Committee, which is to co-

operate with the Health Conservation Association of Kansas City in a program to survey facilities for the prevention of heart disease and to handle cardiac patients.

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Dr. Fredeick A. Willius (Fellow) of the Mayo Clinic addressed the Omaha-Douglas County Medical Society at Omaha, Nebr., January 22, on "Digitalis in Clinical Medicine."

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Dr. Lester J. Palmer (Fellow), Seattle, Washington, addressed the King County Medical Society, February 4, on "Simple Method of Preparation of Dextrose for Intravenous Administration."

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The annual meeting of the East Mississippi Medical Society at Meridian on December 18, 1928, was addressed by the following Fellows:

Dr. Allan Eustis, New Orleans, "Myocardial Insufficiency."

Dr. James S. McLester, Birmingham, "Constipation."

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Dr. Charles Holbrook (Fellow), New Orleans, Louisiana, spoke on "Newer Methods of Treating Syphilis of the Nervous System" before the South Mississippi Medical Society at Laurel, December 13, 1928.

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Dr. Herman Trossbach (Fellow), Bogota, New Jersey, has been appointed Director of the Medical Service of the Hackensack Hospital.

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Dr. Clyde L. Cummer (Fellow), Cleveland, Ohio, was recently elected Chairman of the Board of Trustees of the Cleveland Medical Library Association.

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Dr. Charles W. Stone (Fellow), Cleveland, Ohio, addressed the Sandusky County Medical Society recently on "Psychologic Healing in Antiquity."

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Dr. John D. Dunham (Fellow), Columbus, Ohio, addressed the Columbiana County Medical Society, December 4, 1928, on "Methods and Evaluation of Physical Examination."

Dr. Samuel E. Munson (Fellow), Springfield, Illinois, addressed the Adams County Medical Society, February 11, on "Hypertension."

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The following appointments of Department Heads for 1929 and 1930 at the City Hospital, Cleveland, have been recently announced by the Dean of the Western Reserve University School of Medicine:

Dr. Charles W. Stone (Fellow), Neuropsychiatry.

Dr. Howard T. Karsner (Fellow), Pathology.

Dr. Joseph C. Placak (Fellow), Tuberculosis.

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Dr. Edward L. Tuohy (Fellow), Duluth, Minnesota, addressed the Minnesota Academy of Medicine, February 13, at Saint Paul.

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Dr. Charles H. Neilson (Fellow), St. Louis, Missouri, presented a paper on "Preparation of the Patient for Operation from the Standpoint of the Internist" before the Randolph-Monroe County Medical Society, December 20, 1928.

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Dr. John H. Musser (Fellow), New Orleans, Louisiana, addressed the Nashville Academy of Medicine (Tennessee), February 5, on "Throat Infections in General Medicine."

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Dr. Thomas Hall Shastid (Fellow) is author of an article "My Father Knew Lincoln" in the Nation for February 20, 1929. In this article there occurs an interesting explanation of a peculiarity of Lincoln's physiogmomy that has never been previously noted. "There was one point that my father had noted about Lincoln's physiognomy that I have never seen recorded. It was that the left eye, from time to time, looked queer and then suddenly "crossed," i.e., turned up. At the time when my father told me this it did not strike me as having the least importance. Older grown, however, and become an oculist, I was struck one day by the recollection and then by the meaning of the fact itself. Lincoln had

been the victim of hyperphoria (a *tendency* of one eye upward) with, now and then, a momentary hypertropia (actual *turning* of one eye upward). Such a condition, as all oculists know, gives rise to an intense form of eyestrain and is one of the commonest causes of deep and protracted melancholy—the chronic, inexpressible blues. Here, then, was the probable explanation of the well-known Lincolnian depression of spirits which lasted, off and on, until his death."

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## DR. WARTHIN TO BE HENRY RUSSEL LECTURER

This year the oppointment as Henry Russel Lecturer of Dr. Aldred Scott Warthin, Michigan's distinguished Professor of Pathology, has been announced. The roll of honor of previous Henry Russel Lecturers consists of Professor Moses Gomberg, in 1926; Professor Frederick G. Novy, in 1927; and Professor Henry Arthur Sanders, in 1928. The Henry Russel Award has gone in past years to Assistant (now Associate) Professor Carter Goodrich of the Department of Economics, in 1926; Assistant Professor Albert Hyma of the Department of History, in 1927; and Assistant Professor Laurence M. Gould of the Department of Geology, now with the Byrd Antarctic Expedition, in 1928. The winner of the Award for 1929 will be announced at the time of the Lecture, in May. Michigan, too, has its own "Nobel Prizes" in the Henry Russel Lectureship and the Henry Russel Award, derived from the endowment fund bequeathed to the University by the late Mr. Henry Russel of Detroit.

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## BRIEF REPORT OF THE BOSTON CLINICAL SESSION

The Thirteenth Annual Clinical Session of the American College of Physicians was held at Boston, April 8-12, 1929. The meeting has been acclaimed as the largest and one of the most successful sessions that the College has ever conducted. There were 1464 official registrations, physicians being present from every State in the United States, with the exception of Nevada. There were, in addition, attendants from various Provinces of Canada, from Panama, Colombia (South America), England, Italy, Denmark and China.

The program was divided between clinics in the various Boston hospitals each morning, and general sessions in the afternoon and evening in the Assembly Hall of the Hotel Statler.

The clinics were reported to be of unusual merit with interest, particularly because patients were shown generally. The general sessions, during the afternoons and evenings, were diversified in content and participated in by the leading authorities of the country.

The commercial exhibits were of more than average merit and were splendidly arranged in the foyer of the general assembly hall, where attendants at the session could conveniently examine new publications, pharmaceutical products and apparatus, when coming and going from the general meetings. The effort was to secure, not a large number of exhibitors, but a selected group whose products would be of especial interest to the members of the College.

One hundred and ninety three new members were elected to Fellowship by the Board of Regents and about two hundred and fifty inducted at the Convocation on Friday evening, April 12. Fifty-four physicians were elected to the Associate group.

A special feature was the conferring of five Masterships on Fellows of the College in recognition of their positions of influence and honor an eminence in practice, or of medical research and distinguished service to the College. Those to whom Masterships were conferred were: Alfred Stengel, Philadelphia, Pa.; Charles F. Martin, Montreal, Que.; Charles G. Jennings, Detroit, Mich.; Aldred Scott Warthin, Ann Arbor, Mich.; Frank Smithies, Chicago, Ill.

The names of those elected to Fellowship and to Associateship will be published in a later number.

The new Officers of the College for 1929-30 are: President, John H. Musser, New Orleans, La.; President Elect, Sydney R. Miller, Baltimore, Md.; 1st Vice President,

Aldred Scott Warthin, Ann Arbor, Mich.; 2nd Vice President, F. M. Pottenger, Monrovia, Calif.; 3rd Vice President, Logan Clendening, Kansas City, Mo.; Treasurer, Clement R. Jones, Pittsburgh, Pa.; Secretary General, George Morris Piersol, Philadelphia, Pa.; Executive Secretary, E. R. Loveland, Philadelphia, Pa.

New members of the Board of Regents, elected for three years are: David P. Barr, St. Louis, Mo.; Arthur R. Elliott, Chicago, Ill.; Noble Wiley Jones, Portland, Ore.; Maurice C. Pincoffs, Baltimore, Md.; S. Marx White, Minneapolis, Minn.

New members of the Board of Governors, not heretofore members of that Board, elected for a period of three years, included the following: William Gerry Morgan, Washington, D. C.; Roger I. Lee, Boston, Mass.; Edward B. McCready, Pittsburgh, Pa.; J. O. Manier, Nashville, Tenn.; Charles Edward Riggs, U. S. Navy; Hugh Cumming, U. S. Public Health Service; Harvey Beck, Baltimore, Md.; A. Comingo Griffith, Kansas City, Mo.; C. H. Cocke, Asheville, N. C.; E. J. G. Beardsley, Philadelphia, Pa.; James G. Carr, Chicago, Ill.; Harlow Brooks, New York, N. Y.; Hans Lisser, San Francisco, Calif.; C. H. Beecher, Burlington, Vt.